Original Research Article

A comparison of rheumatoid arthritis patients in Kuwait with other populations: results from the KRRD registry

ABSTRACT

Objective: Data on rheumatoid arthritis (RA) in Kuwait and The Middle East is scarce. Available data from Western countries may not be representative of the region. We describe RA patients in Kuwait and compare them with other RA populations and with Kuwaiti general population.

Methods: Adult RA patients from Kuwait Registry for Rheumatic Diseases (KRRD), the first RA registry in The Middle East, were studied from February 2013 through February 2015. Demographic, clinical and serologic data were compared with other RA populations and with Kuwaiti general population.

Results: 835 patients were enrolled, 62.3% female. Mean age 50.6±12 years and disease duration 6.1±6 years. RA was diagnosed at a mean age of 44.9±12 years. 17.1% had family history of autoimmune rheumatic diseases. 3.1% had rheumatoid nodules. Rheumatoid factor (RF) and anti-citrullinated peptide (ACPA) were detected in 75.6% and 57.8%, respectively. Both were positive in 49% (r=0.287, *p*=0.001). ANA was positive in 19.1%. Both ACPA and a combination of positive RF and ACPA were more in males (*p*=0.017, 0.004 respectively), whereas ANA was more in females (*p*=0.01). One third of male patients were smokers versus 1.9% of females. Smoking was correlated to RF (*p*=0.009) and ACPA (*p*=0,002). Difference in ACPA between genders was statistically explained by the predominance of smoking in males. Comorbidities included diabetes mellitus (DM) (20.8%), hypertension (20.2%), hyperlipidemia (10.5%) and coronary artery disease (CAD) (3.1%). 4 cases of cancer were reported.

Conclusion: RA population in Kuwait includes less women than other RA populations but more than Kuwait general population. Family history is more common. A higher positive ACPA in males was explained by smoking difference. Hypertension and hyperlipidemia were less reported than in both Kuwaiti general population and other RA populations. CAD was similar to other RA populations. DM was more reported, reflecting its high background prevalence in Kuwait.

Keywords: Rheumatoid arthritis, comorbidities, prevalence, registry, KRRD, Kuwait, Middle East, Arabs.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown etiology that causes symmetrical, inflammatory polyarthritis, significant morbidity and premature mortality [1,2]. The prevalence of RA in Kuwait is 1% [3], which is comparable to the overall world figures [4,5]. Yet, descriptive data on RA patients in Kuwait, like the rest of The Middle East, is scarce [6].

This study describes the most important epidemiological and serological features of patients with RA in Kuwait based on results from the new Kuwait Registry for Rheumatic Diseases (KRRD), the first ongoing

registry on RA patients in The Middle East. In addition, we describe the prevalence of common comorbidities and compare our results with those from non-Middle Eastern studies. This evaluation raises questions for future studies and improved care for RA in the Middle East.

2. PATIENTS

Patients were participants in KRRD, a national registry that includes adult patients with rheumatic diseases. Patients who satisfied the ACR criteria for RA [7] registered from February 2013 through February 2015 were studied. They were recruited from the rheumatology departments of four out of the six major government hospitals in Kuwait. These four hospitals are distributed in different governorates in the country covering the ethnic diversity of the Kuwaiti population. Although patients with rheumatic diseases can visit a few small private clinics, patients with RA are usually referred to one of the major government hospitals to receive treatment as medicine is provided free of charge for Kuwaiti residents and at a trivial cost for non-Kuwaitis. If biologic therapy is indicated it is provided at no cost by the Ministry of Health for Kuwaitis and through the Patients Helping Fund Society for non-Kuwaitis.

3. METHODS

Demographic and baseline medical data were obtained including comorbid conditions at presentation. Patients were then followed and clinical and laboratory data were regularly recorded during their hospital visits including data on disease activity and treatment tolerability.

Data were collected by nurses and rheumatologists who were trained to fill a standard form either manually or electronically. The demographic data, disease duration and comorbid diseases were obtained from the patient's medical record as such data is available in all medical records at all the recruiting centers. In addition, during the interview, the patients were also asked by the investigators about the presence of comorbid diseases to enhance the accuracy of the data. Smoking and family history were also obtained through the interview. Family history was considered positive if at least one first degree relative was diagnosed with an autoimmune rheumatic disease.

The nurses were given an educational course in RA and intensive training courses in the determination of tender and swollen joints. The physician's global assessment of disease activity was assessed by the rheumatologist.

Serological data were collected from the patient's medical record. Methods used to measure the selected serological tests were standard across the laboratories in the recruiting centers. IgM rheumatoid factor (RF) was quantitatively measured by nephelometry and measurements above 20 were considered positive. IgG anti-citrullinated peptide antibody (ACPA) was determined by use of the Enzyme-linked Immunosorbent Assay (ELISA) with a cutoff point of 20 U/ml. Anti-nuclear antibodies (ANA) was assessed by use of indirect immunofluorescence using HEp-2 cell line and was considered positive when titer was more than 1:40.

Informed consent was obtained from all study subjects. The data was entered and stored in a secured computer program which linked the collaborating hospitals. It was designed to be used for the registry and approved by the ethics committees of The Faculty of Medicine, University of Kuwait and The Ministry of Health in Kuwait.

To compare our results with other RA populations, large recognized registries from different countries were selected including those from The United Kingdom, Germany, Switzerland and United State of America. Several large studies were also included, the majority were population-based, multicenter or large cohort studies. Using the same laboratory techniques for the serological tests included was also taken into consideration upon selecting the cited studies.

To compare KRRD population with the general population of Kuwait, all studies ever done on the Kuwaiti population and data from resource centers in the designated fields were selected and results were compared where applicable.

4. STATISTICAL ANALYSIS

Descriptive data analysis was used to evaluate means, standard deviation, percentages, histograms and frequency distributions for each variable of interest. Chi square test was used to assess the relationship between two categorical variables, e.g., RF and ACPA. A subcategorical analysis between the genders was made using two-sided independent Student's t-test for age and Chi square test for smoking, RF, ACPA, a combination of RF and ACPA and ANA. Baron & Kenny method [8] was used to examine mediation through a series of regressions to study the relation between smoking, ACPA and gender.

The appropriate statistical procedures were selected according to guidelines [9,10]. SPSS for Windows Statistical Package, Release 22, was applied for all the statistical procedures.

5. RESULTS

5.1 Demographic and serological characteristics

A total of 835 patients were enrolled in the registry. The majority were female (62.3%) (table 1). The mean age was 50.6 ±12 years, ranging between 15 and 96 years and the mean disease duration was 6.1±6 years. The diagnosis of RA was diagnosed at a mean age of 44.9±12 years, ranging between 8 and 73 years. About 17% of the patients reported at least one first degree relative with an autoimmune rheumatic disease, the commonest being RA. Rheumatoid nodules were not common being present in only 3.1%.

Table 1. A descriptive analysis of RA patients enrolled in the registry.

Characteristic	N	N studied*
Female	520 (62.3%)	835
Mean age ± SD (range)	50.6 ±12 (15-96)	835
Mean age at diagnosis ± SD (range)	44.9±12 (8-73)	717
Mean RA duration in years ± SD (range)	6.1±6 (0-46)	717
Smoking	46 (9.2%)	500
Positive F/H**	114 (17.1%)	667
Rheumatoid nodules	22 (3.1%)	701
RF positive	576 (75.6%)	762
ACPA positive	398 (57.8%)	689
RF & ACPA positive	330 (49%)	673
ANA positive	131 (19.1%)	686

** Numbers less than 835 reflect missing data. **The presence of at least one first degree relative with an autoimmune rheumatic disease. SD= standard deviation. F/H= family history. RF=rheumatoid factor. ACPA=anti-citrullinated peptide antibodies. ANA=anti-nuclear antibodies.*

With regard to serology, RF was positive in 576/762 patients (75.6%) and ACPA was positive in 398/689 (57.8%). Among patients who were tested for both RF and ACPA, 330/673 (49%) were found to have both tests positive versus 114 (16.9%) who had them both negative (table 2). As expected, RF and ACPA were significantly correlated, p=0.001. ANA was found to be positive in 19.1% of the study population.

Table 2. Association between RF and ACPA.

	RF positive	RF negative	Total	Test Statistics
ACPA positive	330 (49%)	57 (8.50%)	286 (42.5%)	X^2_2=54.806, r=0.285, p<0.001
ACPA negative	172 (25.60%)	114 (16.9%)	387 (57.50%)	
Total	502 (74.60%)	171 (25.40%)	673 (100%)	

RF=rheumatoid factor. ACPA=anti-citrullinated peptide antibodies.

5.2 Differences in characteristics between the genders

A subgroup analysis between the genders showed no significant difference in age or age at diagnosis (table 3). However, ANA was more frequent in females with RA, with no significant correlations with the variables RF, ACPA and a combination of RF and ACPA.

A marked difference was observed in number of smokers at entry, as approximately one third of male patients were smokers versus only 1.9% of females (p<0.0001).

Although RF positivity was not different between the genders, ACPA was more frequent in male patients (p=0.017). Similarly, a combination of a positive RF and a positive

ACPA was more frequent in male patients (p=0.004).

Table 3. A comparison between female and male patients.

Characteristic	Females	Males	X^2_2	p-value
Age (mean + SD)	50.6±12	50.2±11		0.522
Age at diagnosis	45.7±12	43.9±12		0.072
Smoking N(%)	7/372(1.9%)	39/128(30%)	93.16	<0.0001*
RF positive N(%)	355/478(74.3%)	221/284(77.8%)	1.22	0.27
ACPA positive N(%)	231/426(54.2%)	167/263(63.5%)	5.73	0.017*
RF&ACPA positive N(%)	185/415(44.6%)	145/258(56.2%)	12.01	0.004*
ANA positive	97/430(22.6%)	34/256(13.3%)	9.17	0.01*

*SD=standard deviation. RF=rheumatoid factor. ACPA=anti-citrullinated peptide antibodies. ANA=anti-nuclear antibodies. *P<0.05.*

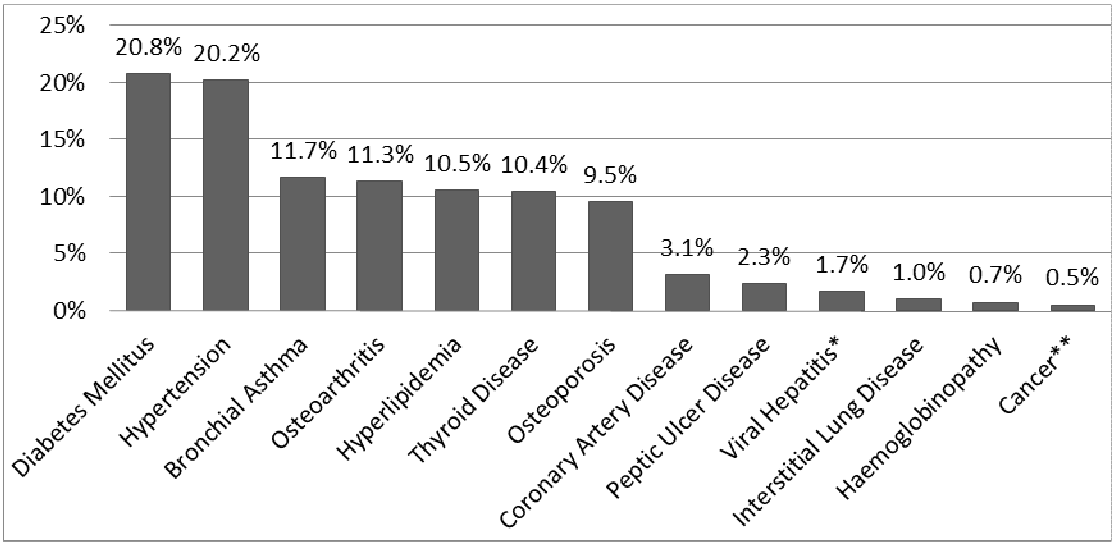
5.3 Effect of smoking on serology

Since both smoking and ACPA were significantly different between the genders, further analysis was performed to study whether smoking has a role in the presentation of ACPA in male gender. Smoking was significantly correlated to both RF (p=0.009) and ACPA (p=0.002). A mediation analysis was conducted. Baron & Kenny method was used to examine mediation through a series of regressions. First, regression with smoking predicting ACPA was significant, F(1,430)=9.735, p=0.002 with regression weight (ß=0.259, p= 0.002). Regression with smoking predicting gender was conducted next which was significant, F(1,498)=114.040, p<0.001, suggesting that smoking was related to gender. Regression with smoking and gender was conducted last which was also significant, F(2, 428)=4.906, p=0.008. This suggests that both smoking and gender predict ACPA independently. Considering these results, it is concluded that mediation is supported and that the difference in ACPA between the two genders can be explained by the higher prevalence of smoking in males.

5.4 Comorbid diseases

With regard to comorbid diseases reported at entry of the registry, diabetes mellitus (DM) was the commonest, found in 174 patients (20.8%), followed by systemic hypertension in 169 patients (20.2%) (figure 1). Hyperlipidemia was found in 88 patients (10.5%) and coronary artery disease in 26 patients (3.1%). Bronchial asthma and thyroid diseases were found in 98 patients (11.7%) and 87 patients (10.4%), respectively. Ninety four patients (11.3%) were diagnosed with osteoarthritis whether primary or secondary and 79 (9.5%) with osteoporosis. Three cases of solid cancers (two bladder and one thyroid) and one lymphoma were reported at entry (0.5%).

Figure 1. Prevalence of comorbidities in RA patients.



**10 patients with hepatitis C virus and 4 with hepatitis B virus. **2 patients with bladder cancer, 1 thyroid and 1 lymphoma.*

5.5 A comparison of patients characteristics with other populations

Table 4 shows a comparison between RA patients in KRRD and other RA populations in the literature. The ratio of female to male gender was lower than in other RA populations, but higher than the adult general population of Kuwait where 41.8% are females [11]. Patients in KRRD were slightly younger than

RA populations in the cited studies, possibly because of a shorter disease duration as RA was diagnosed at a similar age in both studies.

Positive family history of autoimmune rheumatic diseases was reported more frequently than in the literature in spite of including all autoimmune diseases in the cited studies in contrast to KRRD where only autoimmune rheumatic diseases were reported.

The prevalence of RF, ACPA and the significant correlation between the two tests were similar to that in many studies [30-33]. The combination of a positive RF and a positive ACPA were also similar to other studies where the same laboratory technique was used. However, the higher prevalence of ACPA and a combination of RF and ACPA in the male gender was not reported in other studies [34]. ANA was positive in 19.1% of the studied population, similar to other studies, although in the cited studies a higher positive cut-off point was used, 1:100 and 1:160, using the same laboratory technique.

Table 4. A comparison of patients characteristics between the KRRD study population and other major studies or registries.

Characteristic	Present study	Other studies
Females	62.3%	67-78%[12-23]
Mean age of patients (years)	50.6	53-60[12-20]
Mean age at diagnosis (years)	44.9	42-54[12-15,17, 19-24]
F/H of rheumatic disease	17.1%	10.2%[25]*
Positive RF + ACPA	49%	50%[26], 63%[27]
Positive ANA	19.1%	16.7-37.5%[28,29]

**Family history of any autoimmune disease was included in the comparison studies versus only autoimmune rheumatic diseases in KRRD. F/H=family history. RF=rheumatoid factor. ACPA=anti-citrullinated peptide antibodies. ANA=anti-nuclear antibodies.*

5.6 A comparison of comorbidities with other populations

With regard to comorbidities (table 5), smoking was found to be lower than in other studies and lower than Kuwait general population, However, when smoking is stratified according to gender, it appears that smoking is much more common in males than in females in the KRRD RA population (30% versus 1.9%) as it is the case in Kuwait general population (34% versus 1.9%) [35-36], a picture which is probably unique to our area, as compared to other parts of the world [45].

Hypertension was less frequent than in the general population of Kuwait (20.2% vs 26.3%) where age and gender distribution in the selected Kuwait general population was similar to that of KRRD population. Hypertension in KRRD was also less prevalent than in RA population in a large international study (20.2% vs 40%0 [37] although female gender was more predominant and the mean age was five years higher as compared to KRRD population.

Likewise, hyperlipidemia was lower than in other RA populations (10.5% vs 14%-31.7%) and the population of Kuwait (10.5% vs 22.2%).

DM, on the other hand, was more frequent than in other RA populations (20.8% and 8-15% respectively), but not very different than the general population of Kuwait which is known for its high prevalence of DM (21.4%).

Coronary artery disease (CAD) was similar to other RA patients in other studies (3.1% vs 3.2-4%).

Table 5. A comparison of frequencies of common comorbidities between the present study, RA populations in international studies and Kuwait general population.

Comorbidity	Present study*	RA population in international studies*	Kuwait general population
Smoking	9.2%	15-31%[12-15,17,24]	17.95[35,36]
Hypertension	20.2%	40%[37],32%[38]	26.3%[39]**
Hyperlipidemia	10.5%	14%[38],31.7%[37]	22.2%[40]***
Diabetes mellitus	20.8%	11%[41],8%[38],15%[37]	21.4%[42,36]***
Coronary artery disease	3.1%	3.2%[38],4%[37]	N/A
Thyroid disease	10.4%	7%[43],10.9%[44]	N/A

**Either patient's interview or medical records or both were used to obtain data. **Hypertension was defined via blood pressure measurement. ***Laboratory testing was used to obtain data. N/A=not available.*

6. DISCUSSION

Epidemiological and serological features of RA patients in Kuwait were described. Some of these features were found to be unique to our area whereas others were similar to RA patients in other countries. Such comparison is interesting as data on RA population in The Middle East is scarce.

Genetic factors may explain the higher prevalence of a family history of autoimmune rheumatic diseases. The common tradition of arranged marriage especially between relatives including cousins may facilitate the transmission of potential genes. Although the exact etiology of RA is unknown, it has been shown that genetic heritability was roughly 60% [46]. Genetic and family clustering of the disease warrant further studies to explore possible disease transmission across the family members in our area. In addition, clustering of other autoimmune diseases may also necessitate further exploration as such diseases have been found to be more prevalent in family members of RA patients [44-46]. HLA gene and other susceptibility genes for RA were found to be shared by some other autoimmune diseases and may explain the above findings [50].

The overall low prevalence of smoking in Kuwait reflects the very low prevalence of smoking in females in our area where smoking is identified as a male specific habit and is less socially acceptable for females. Smoking is now recognized as an important factor in the etiology and the severity of RA as the odds ratio was found to be 1.56 in one study [51]. The relative risk [RR] was found to be 1.4, up to 2.2 in people who have smoked more than 40 pack-years [52], in addition to being an important risk factor for cardiovascular diseases [53].

Our study confirmed the previously suggested correlation between ACPA and smoking [54-55]. A meta-analysis previously showed that the combination of smoking and shared epitope resulted in a higher risk of ACPA, suggesting a strong gene–environmental interaction between smoking and shared epitope in the development of ACPA in patients with RA [56]. A multi-cohort study indicated that the effect of smoking on joint damage is mediated via ACPA and that smoking is not an independent risk factor for

radiological progression in RA [57]. The discrepancy in smoking between the genders in Kuwait, in addition to its possible role in the presentation of ACPA in males, may explain the relatively lower ratio of female to male genders as compared to other populations. It should be further studied whether this affects the presentation, the severity and the prognosis of the disease in this particular gender as ACPA has been considered as one of the factors that play a role in the severity and the prognosis of the disease [58-61].

Although hyperlipidemia was found to be lower than the general population of Kuwait, the difference in hyperlipidemia between RA and non-RA populations remains debatable in the literature [51,62].

The high prevalence of DM among RA patients in Kuwait is not surprising since Kuwait is ranked as one of the top five countries in the world with regard to the incidence of diabetes in the adult population [63]. While DM was increased in RA patients from Europe and the US compared to the general population [64-66], this was not the case in the KRRD registry.

One of the factors that may have affected the relatively lower prevalence of hypertension and hyperlipidemia in KRRD is the young age of RA population in KRRD. A shorter disease duration may explain their relatively young age as compared to other RA populations. A higher standard of care in terms of CAD risk factor screening and treatment and a regular medical checkup of the patients may explain the lower prevalence of some comorbidities as compared to the general population of Kuwait, although other factors that may contribute to this should be studied. Even though hypertension and hyperlipidemia were less frequent in KRRD patients, screening for and controlling CAD risk factors, in particular DM, must always be considered as an important part of RA management and of awareness campaigns against the disease, as CAD contributes markedly to the morbidity and mortality of RA [67].

One of the possible limitations in our study is the recall bias in collecting some of the data such as family history. In addition, when comparing hyperlipidemia with the general population of Kuwait, the method of defining hyperlipidemia was different as it was through patient interviews and medical records in KRRD versus blood level measurement in the contrast study.

7. CONCLUSION

Data from KRRD, the first and the largest RA registry in The Middle East, have shown that RA population in Kuwait includes less women than other RA populations but more than Kuwait general population. Family history is more common than in other RA populations. A higher presence of positive ACPA among males were statistically explained by the higher frequency of smoking in that gender. In spite of hypertension and hyperlipidemia being less commonly reported, CAD was similar to other populations and to the general Kuwait population. DM, on the other hand, was more prevalent than in other RA populations reflecting its high background prevalence in Kuwait. Given the paucity of data describing RA patients in our region, these findings raise questions for future studies and improved care for RA in the Middle East.

DISCLOSURE:

This is an investigator study from KRRD registry. The KRRD registry is supported by unrestricted grants from Pfizer and Hoffmann-La Roche.

ETHICAL APPROVAL

The authors have obtained an ethical approval from the ethics committees of The Faculty of Medicine, University of Kuwait, The Ministry of Health in Kuwait and Kuwait Institute for Medical Specialization (KIMS).

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