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Renal dysfunction among rheumatoid arthritis patients: A retrospective cohort study

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a common rheumatological disease which can involve a variety of different renal manifestations. This may be explained by disease effect itself or by medications used for treatment that may lead to renal dysfunction and its complications.
We aimed to identify the prevalence and factors that played a role in renal dysfunction among RA Jordanian patients.
Method: 285 patients with RA visiting outpatient clinic between March 2016 and March 2017 were included in a retrospective study design. Age, gender, comorbidities, duration of the disease, medications and laboratory results were gathered and scoring of RA activity was done.
Results: Data gathered from the 285 patients showed a female predominance with 88.4% female and 11.6% male. The average disease duration was 6.7 years. Age, DM, HTN, and serum CRP were associated with worse renal function on univariate analysis. 44 patients (18.8%) presented with microscopic hematuria, 16 (6.9%) with proteinuria and only 5 (2.1%) patients presented with both microscopic hematuria and proteinuria. Patients with eGFR <60 ml/min had longer disease duration with a mean of 11 years (±7.7) in comparison to 6.4 years (±6.1) for those with eGFR>90 ml/min (P = 0.001).
Conclusion: Renal dysfunction is not common in RA Jordanian population and has variable presentations. Age and the duration of illness play a major role in the progression of CKD if present. Future prospective studies evaluating renal biopsies in RA patients are needed.

1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune disorder characterized by inflammation of multiple synovial joints but has multiple extra-articular manifestations as well including kidney involvement. Alawneh et al. reported a higher sever disease rate and a lower remission rate in Jordanian RA patients [1].

RA can affect the kidneys directly by effect of the disease itself or secondary to the drugs used for treatment; including biological and non-biological disease modifying anti-rheumatic drugs (DMARDS) [2–4] or analgesics like non-steroidal anti-inflammatory drugs (NSAIDs).

Clinico-pathological correlations showed that the most common pathological findings on renal biopsy in patients with RA were secondary amyloidosis, membranous nephropathy, and less commonly rapidly progressive glomerulonephritis [5–7].

We aimed to identify the prevalence and factors that played a role in renal dysfunction among RA Jordanian patients.

2. Materials and methods

In a retrospective study design, we evaluated all RA patients who presented to the rheumatology clinic in King Abdullah University

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Hospital (KAUH), Irbid, a 650-bed, urban academic tertiary referral hospital, that serves 5 provinces in the north of Jordan. Between March 2016–March 2017.

The study was approved by the Institutional Review Board of Jordan University of Science and Technology and King Abdullah University Hospital. The study was conducted and reported in line with STROCSS criteria [8].

The protocol had been registered at research Registry with the unique identification number researchregistry6050.

The study included patients who were diagnosed with RA according to the 1987 revised American College of Rheumatology classification criteria [9] as it was suggested to be more specific and can predict more erosive disease than the 2010 classification [10,11]. Patients had at least one year follow up in the clinic.

Data collected using our electronic records included: patients' demographics, duration of the disease, presence of comorbidities, and disease related disabilities. Active RA-related medications were recorded as well. Laboratory data included erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), serum creatinine, and urine analysis. The presence of Rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (Anti-CCP) was recorded and patients were labeled as either positive or negative based on the laboratory reference values.

Rheumatoid arthritis disease activity at the time of study enrolment was assessed using both: Disease Activity Score in 28 joints (DAS28) and Clinical disease activity index (CDAI). DAS28 combines data on the presence of swelling and tenderness in 28 joints, ESR and patient global health. CDAI includes tender and swollen joint counts in 28 joints examined in addition to the patient's and physician's global estimate of disease activity (on a 0–10-cm visual analog scale).

Patients were stratified according to the disease activity into four categories based on the DAS28 and CDAI scores, using the worse score when data did not correlate. Remission was categorized as DAS 28 $\leq$ 2.6 or CDAI $\leq$2.8; low disease activity was categorized as DAS 28 $\leq$ 3.2 or CDAI $\leq$10; moderate disease activity if DAS 28 $\leq$ 5.1 or CDAI$\leq$ 22; high disease activity if DAS 28 $>$ 5.1 or CDAI $>$22 [12].

Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology equation (CKD-EPI) [13].

Renal involvement was defined as the presence of hematuria, and/or $\geq$ +1 proteinuria on dipstick urine analysis on at least 2 occasions 3 months apart, and/or eGFR of $<$60 ml/min [7,14]. Renal biopsies; indications and results were also recorded.

Hypertension (HTN) was defined as the use of at least one oral antihypertensive drug and/or systolic blood pressure $>$140 mmHg or diastolic blood pressure $>$90 mmHg [15,16].

Diabetes mellitus (DM) was defined as the use of oral hypoglycemic agents and/or insulin therapy.

2.1. Statistical analysis

Data was described using a mean and standard deviation (±SD) for continuous variables and percentages for categorical variables. The means of continuous variables were assessed using independent student's *t*-test and chi-square test for the categorical variables.

Multivariate logistic regression analysis was used to evaluate the association of renal dysfunction as a dependent variable and different independent variables considered to be significant risk factors in univariate analysis as well as factors that were considered clinically significant. All analyses were performed using STATA/MP, version 14.0 (Stata Corp LLC, College Station, TX, US).

3. Results

A total of 285 patients with rheumatoid arthritis were included in the study. The mean age of patients at time of enrollment was 54.5 years. A female predominance was observed with the percentile of female and males included; 88.4% and 11.6% respectively, for baseline characteristics see Table 1.

Six patients (2.1%) were found to have renal dysfunction (proteinuria, hematuria and eGFR $<$60 ml/min). These patients were noted to have longer disease duration with a mean of 11 years (±7.7) compared to 6.4 years (±6.1) in those with eGFR $>$90 ml/min (P = 0.001). The eGFR was found to have an inverse correlation with age, see Table 2 for baseline characteristics based on eGFR. Serum CRP, DM, and HTN were associated with worse renal function on univariate analysis.

Forty-four patients (18.8%) presented with microscopic hematuria, 16 (6.9%) with proteinuria and only 6 (2.1%) with both microscopic hematuria and proteinuria. No association was found between RF positivity and both microscopic hematuria or proteinuria with P values of 0.85 and 0.2 respectively. Although patients that presented with hematuria or proteinuria were found to have moderate to high DAS 28 or CDAI scores, no significant correlation between these scores and renal dysfunction was found. The mean DAS 28 score for patients with proteinuria and microscopic hematuria was 4.5 ± 1.6, and 4.9 ± 1.5 respectively while the mean CDAI score was 16.7 ± 10.5 and 21.9 ± 14.2. P values for association between DAS 28 and each proteinuria & microscopic hematuria was 0.42 and 0.88 respectively. While for CDAI it was 0.47 and 0.63 respectively.

Comparing disease activity by scoring system showed; 26 patients (9.1%) in remission by DAS 28 vs 20 (7%) by using CDAI, 19 (6.7%) vs 59 (20.7%) with low activity, 108 (37.9%) vs 102 (35.8%) with moderate activity and 132 (46.3%) vs 97 (36.5%) with high disease activity.

As for DM patients, 5 patients had microscopic hematuria (P = 0.68) and only 1 patient had proteinuria (P = 0.87). For HTN patients, 8 had microscopic hematuria (P = 0.83) while none of the hypertensive patients had proteinuria.

On multivariate analysis, only age (OR 1.1, P $<$ 0.001) and CRP (OR 1.2, P $<$ 0.001) were significantly associated with worse kidney function, see Table 3. Other factors like gender (OR 0.6, P = 0.48), urinary protein (OR 1.0, P = 0.08) and disease activity scores were not predictors of renal dysfunction.

At presentation, 48.2% were on different dosages of NSAIDs for joint pain, 235 (82.5%) patients were on glucocorticoids, 106 patients (37.2%) were on Sulfasalazine (SSZ), 3 (1%) on Leflunomide, 6 (2.1%) on Infliximab, 27 (9.5%) on Etanercept, 26 (9.1%) on Adalimumab, 29 (10.2%) on Rituximab, 16 (6.9%) on Methotrexate (MTX), 8 (2.8%) on Azathioprine, and 26 (11.1%) patients continued on NSAID's. For the choice and details regarding drugs used for treatment see Table 4.

At last follow up, 32 (13.7%) patients had microscopic hematuria, 22 (9.4%) with proteinuria, and 7 (3%) with both microscopic hematuria and proteinuria. eGFR at last follow up was 93.2 ml/mi (±22.3) compared to 97.1ml/min at presentation.

Table 1
Baseline characteristics.

Variable	N (%)
Age, mean (±SD)	54.5 (±14.8)
Gender: Male	33 (11.6%)
Female	252 (88.4%)
Diabetes Mellitus	48 (16.8%)
Hypertension	71 (24.9%)
ACEi †/ARB ‡	24 (9.1%)
§ eGFR by CKD-Epi (±SD), ml/min	97.1 (±22.5)
¶ DAS 28 (±SD)	4.8 (±1.5)
|| CDAI (±SD)	19.6 (±13.4)
†† ESR (±SD), (Normal range 0.0–20.0 mm/1 h)	42.0 (±22.9)
‡‡ CRP (±SD), (Normal range 0.0–5.0 mg/l)	49.9 (±79.5)
Rheumatoid factor, n (%)	125 (43.8%)
φ Anti-CCP, n (%)	115 (40.3%)

† ACEi – angiotensin converting enzyme inhibitor, ‡ ARB – angiotensin receptor blocker, § eGFR-estimated glomerular filtration rate, ¶ DAS 28 - Disease Activity Score in 28 joints, || CDAI - Clinical Disease Activity Index, †† ESR - erythrocyte sedimentation rate, ‡‡ CRP - C-Reactive protein, φ Anti-CCP - anti-cyclic citrullinated peptide antibody.

Table 2
Baseline characteristics based on eGFR.

Variable	eGFR ≥90	90 > eGFR ≥60	eGFR <60	P value
Age (±SD)	48.1 (14.2)	60.9 (11.7)	67.8 (16.2)	**0.0001**
Gender: Male	26 (9.1%)	6 (2.1%)	1 (0.4%)	0.65
Female	214 (75.1%)	33 (11.6%)	5 (1.8%)	
Diabetes Mellitus	36 (12.6%)	9 (3.2%)	3 (1.1%)	**0.04**
Hypertension	51 (17.9%)	18 (6.3%)	2 (0.7%)	**0.003**
† DAS 28 (±SD)	4.8 (1.5)	5.0 (1.2)	4.6 (1.9)	0.88
‡ CDAI (±SD)	19.5 (13.6)	21 (11.9)	18 (13.4)	0.82
§ ESR (±SD)	42.1 (23.3)	41.4 (20.2)	42.7 (27.1)	0.97
CRP (±SD)	56.6 (10.4)	76.0 (12.0)	114.8 (17.9)	**0.0001**
Prednisone	193 (82.1%)	36 (15.3%)	6 (2.6%)	0.10
Microscopic hematuria	23 (52.3%)	14 (31.8%)	7 (15.9%)	0.89
Proteinuria	8 (50%)	4 (25%)	4 (25%)	0.22

† DAS 28 - Disease Activity Score in 28 joints, ‡ CDAI - Clinical Disease Activity Index, § ESR - erythrocyte sedimentation rate, ¶ CRP - C-Reactive protein.

Table 3
Factors associated with renal dysfunction.

Variable	Odds ratio (OR)	95% Confidence Interval	P value
Age	1.1	1.0–1.2	<0.001
Hypertension	1.0	0.3–3.4	0.98
Diabetes Mellitus	0.94	0.22–3.8	0.93
C-Reactive protein	1.2	1.1–1.3	<0.001

Table 4
Drug used based on eGFR.

Variable	eGFR ≥90	90 > eGFR ≥60	eGFR <60	P value
Methotrexate, n (%)	208 (82.2%)	39 (15.4%)	6 (2.4%)	**0.034**
Sulfasalazine, n (%)	95 (33.3%)	11 (3.9%)	0 (0%)	0.064
Leflunomide, n (%)	3 (1.1%)	0 (0%)	0 (0%)	0.75
Infliximab, n (%)	6 (2.1%)	0 (0%)	0 (0%)	0.56
Etanercept, n (%)	18 (6.3%)	7 (2.5%)	2 (0.7%)	**0.015**
Adalimumab, n (%)	21 (7.4%)	4 (1.4%)	1 (0.4%)	0.77
Rituximab, n (%)	26 (9.1%)	3 (1.1%)	0 (0%)	0.59
Azathioprine, n (%)	7 (2.5%)	1 (0.4%)	0 (0%)	0.90

4. Discussion

Rheumatoid arthritis (RA) is one of the more common rheumatological diseases worldwide. It can affect 0.5–1% of adults and is characterized by synovitis and systemic inflammation. Fifty percent of cases have a genetic predisposition, in addition to other environmental factors that may increase the risk for the disease [17].

The prevalence of kidney involvement in RA is variable ranging between 20 and 50%, this can manifest primarily as different types of glomerulonephritis (GN) related to the disease process itself, or less commonly as rheumatoid vasculitis and amyloidosis due to a prolonged inflammatory state [18,19].

Medications used for treatment of RA have been associated with kidney damage as well. Types of GN most frequently noted include mesangioproliferative, focal and diffuse proliferative and membranous GN. Nephrosclerosis is the most common finding in autopsies done on rheumatoid arthritis patients. Papillary necrosis and interstitial nephritis can also be seen and are mainly linked to the use of non-steroidal anti-inflammatory drugs (NSAIDs) and penicillamine [20].

When comparing patients with RA with the general population, the prevalence of kidney dysfunction and chronic kidney disease (CKD) is higher. Saisho et al. in Japan using the National Database of Rheumatic Disease (iR-net in Japan-NinJa study 2012) evaluated around seven thousand patients with RA with whom an estimated glomerular filtration rate (eGFR) was available and found that patients had lower eGFR than other general population with different stages of chronic kidney disease [21]. Another two studies from France and Taiwan showed that CKD and renal dysfunction is common in RA patients [22,23].

For evaluation of the early stages of renal dysfunction in patients with RA, the use of serum cystatin C levels and not serum creatinine levels may be helpful [24]. According to Sato et al., it may detect earlier changes in eGFR that may predict cases with secondary amyloidosis in patients with RA [25]. Cystatin C levels may also predict risk of myelosuppression in RA patients secondary to treatment with methotrexate [26].

Early control of the disease might lower the risk of renal involvement and the potential drop in eGFR [27]. Deceleration of eGFR decline in RA patients and hence delaying progression of CKD in these patients can be achieved by use of biologic DMARDs [28]. Control of progression of CKD in RA may help decrease cardiovascular complications and mortality in this population as well [23].

In our study, unlike other studies; we found that renal involvement is not common in RA patients and that advanced age with or without disease activity was the most important factor affecting renal function in these patients. With advanced age; people usually loose nephrons and kidney function with it [29], therefore interpretation of age and kidney function should be handled with caution, having said that, the mean age of our patients is around 54 years, which is according to WHO age group classification considered as young population, hence age alone may not explain renal dysfunction.

CRP likely as an inflammatory marker, marker of disease activity, was also a significant predictor of renal dysfunction in our study [30].

HTN and DM were only significant by univariant analysis. These findings are comparable to other cross-sectional studies from Japan and France [14,22]. However, due to the relatively small number of patients in our study the prevalence of renal dysfunction was lower if compared to others.

With better understanding of the pathogenesis of RA, newer drugs were introduced to treat RA patients who are resistant to the regular regimens. Biological agents improved symptoms and signs of RA as well as helped in preventing bone destruction [31,32].In our study, though the patients number is small; those who received Methotrexate ($P = 0.034$) which is the gold standard therapy for RA [33], and Etanercept ($P = 0.015$) tumor necrosis factor α type II receptor IgG1 fusion protein that suppresses the inflammatory cascade in RA patients [31,34] had better renal function compared to other therapeutic agents.

3 of our patients underwent kidney biopsies for proteinuria, microscopic hematuria and abnormal kidney function; 2 showed IgA nephropathy and one with focal segmental glomerulosclerosis (FSGS). Though our biopsies findings are not a common pathological findings [6], Nakano et al. reported IgA deposition in almost half of their cases with mesangial GN [35]. Same for FSGS, which can be related to drugs used to treat RA like NSAID or as a consequence of inflammatory process related to RA [5].

The low rate of renal biopsies limits the potential to define the exact histopathologic changes of RA with certainty. Whether RA is a cause for end stage renal disease or not couldn't be determined due to small sample and short follow up design.

Our hope is to recruit a larger group of patients in a multicenter prospective designed study with longer follow up to allow us to better define the spectrum of renal involvement, prevalence of renal dysfunction as well as genetic and environmental risk factors for renal disease in RA in our region. This can also assist in determining the best treatment options to delay CKD progression if present. Using kidney biopsies can be recommended for better histological and pathological explanation in patients presenting with CKD and RA.

4.1. Conclusion

Though renal involvement and dysfunction in RA in our study is uncommon; it needs better recognition earlier in the disease course to prevent future renal function loss and to decrease complications and mortality. A prospective studies addressing renal biopsies in RA patients with proteinuria and/or hematuria are needed for better understanding of the disease.

5. Limitations

Though it's the first study from Jordan addressing renal impairment in RA patients; it still a single center study with relatively small size sample.

Ethics approval

The study was approved by the Institutional Review Board of Jordan University of Science and Technology and King Abdullah University Hospital.

Author contribution

A.O conceptualize research idea, data collection, data analysis, literature review, writing the manuscript, S.A literature review, results analysis, interpretation of data, writing the manuscript, K.A literature review, results analysis, writing the manuscript, F.A literature review, results analysis, writing the manuscript, D.A literature review, results analysis, writing the manuscript, D.Z data collection, literature review, writing the manuscript.

Guarantor

Ashraf Oweis.

Trial registry number

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Consent for publication

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

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Declaration of competing interest

The authors declare that they have no competing interests.

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List of abbreviations

RA	Rheumatoid arthritis
CKD	Chronic Kidney Disease
DMARDS	disease modifying anti-rheumatic drugs
NSAIDs	non-steroidal anti-inflammatory drugs
ESR	erythrocyte sedimentation rate
CRP	C-Reactive protein
RF	Rheumatoid factor
Anti-CCP	anti-cyclic citrullinated peptide antibody
DAS28	Disease Activity Score in 28 joints
CDAI	Clinical disease activity index
CKD-EPI	Chronic Kidney Disease Epidemiology equation
eGFR	estimated Glomerular filtration rate
DM	Diabetes mellitus
HTN	Hypertension
GN	glomerulonephritis
FSGS	focal segmental glomerulosclerosis

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2020.11.011.

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