Original Article

Assessment of Renal Involvement in an Iraqi Cohort of Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune chronic systemic inflammatory disease involves synovial joints but may involve extra-articular organ as well. **Objectives:** to determine the prevalence of indicators of renal involvement in patients with RA with implications of impact of related drugs on the kidney. **Materials and Methods:** This cross-sectional study was conducted from May 1, 2019, to November 1, 2019, in the Outpatient Rheumatology Clinic of Hawler teaching hospital, Erbil, Iraq. One hundred and seventy-six patients with seropositive RA were enrolled, other 13 were dropped because of missing data. Participant's characteristics and data regarding drug history were collected. Body mass index (BMI), erythrocyte sedimentation rate (ESR), and serum creatinine were measured; renal function was assessed from the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease formula. Urine examined for proteinuria, microscopic hematuria, and noninfectious leucocyturia. When eGFR <60 ml/min/1.73 m² regarded as renal impairment, impact of RA medications non-steroidal anti-inflammatory drug, disease-modifying anti-rheumatic drugs, and biological agents on renal function and urine sediments were studied. **Results:** Out of a total 176 RA patients, 56.8% were females, their mean age 50.4 (±10.4) years, BMI 28.7 (±3.6) kg/m², with disease duration 8.3(±4.5) years. Renal impairment was detected in 20 (11.4%) participants. Proteinuria, hematuria, and uninfectious leucocyturia were observed in 10.2%, 23.9%, and 25%, respectively. Renal dysfunction was significantly associated with old ages, BMI ≥30, long duration of disease and proteinuria ($P = 0.004$, 0.002, 0.014, and 0.009, respectively). Renal impairment was not significantly associated with sex, smoking status, ESR level, RA medications, hematuria, and uninfectious leucocyturia ($P > 0.5$). **Conclusions:** Renal disorder is common in RA patients. Regular monitoring of renal involvement by using eGFR and urinary dipstick is crucial, especially in the elderly obese RA patients with a long duration of the disease and proteinuria. Early identification of renal disease can facilitate the early intervention and achieve the better management of RA patients.

Keywords: Disease-modifying anti-rheumatic drugs, estimated glomerular filtration rate, proteinuria, renal involvement, rheumatoid arthritis

Introduction

Rheumatic diseases are autoimmune diseases affecting joints and soft tissue with some time extra articular involvement that affects solid organs such as kidneys.[1] There are number of rheumatic diseases can present with renal involvement with different presentations varies from mild to severe, screening of serum and urine parameters for assessing of renal function is mandatory for patients with rheumatic diseases.[2] Renal disease and rheumatic disease are both commonly seen in outpatients, about 18% of rheumatology clinics were reported to have estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73 m² in comparison with the general population which is 5%.[3] Rheumatoid arthritis (RA) is an autoimmune chronic systemic inflammatory disease involves synovial joints but may involve extraarticular organ as well, affects 0.5%–1% population worldwide.[4] Renal involvement in RA patients are caused by either renal toxicity of medications used in RA such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, and methotrexate or secondary renal involvement by the chronic

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inflammatory process of RA such as renal amyloidosis or various types of glomerulonephritis.[5] Despite the presence of various causes of renal involvement in RA patients, the prevalence of renal disorders in RA are too small and the incidence of renal involvement vary depending on the criteria used and the patients population examined, they might present with isolated hematuria or proteinuria or combined hematuria and proteinuria or decrease in eGFR.[6-8] Proper management of RA and judicious use of RA medications could help to reduce other related diseases by reducing shared risk factors and prevalence of systemic manifestations like renal impairment which is serious health problem but treatable disease if caught in the early stages.[9]

The current study designed to determine the indicators of renal involvement in RA patients with implications of impact of RA medications on the kidney.

Materials and Methods

Study design and patients

This cross-sectional study was conducted in the Outpatient Rheumatology Clinic at Hawler teaching hospital, Erbil, Iraq, from May 1, 2019, to November 1, 2019. All patients with confirmed seropositive RA for either or both (rheumatoid factor and Anti CCP antibody) were enrolled in this study, unless they met any of the following exclusion criteria: <18 years of age, those with comorbidities such as diabetes mellitus, hypertension, heart failure, chronic liver disease, history of organ transplant, acute renal failure in past 3 months, receiving renal replacement therapy, having other rheumatic disorders, and being pregnant.

Out of 189 patients met the inclusion criteria, 176 of them enrolled in the study other dropped because of unwillingness or missing data. All participants underwent detailed history and proper physical examination. For each participant, the following data were recorded: age, gender, obesity (body mass index [BMI]: kg/m²), smoking status, duration of the disease, and medication use in the treatment course; disease modifying antirheumatic drugs (DMARDs), biological agents, and intake of NSAIDs during the last 3 months. Laboratory tests include erythrocyte sedimentation rate (ESR) as a parameter of inflammation, serum creatinine (sample was analyzed on COBS-111 machine) as a marker of excretory renal function, for calculation the mean of 2 readings 1 week apart was used. At enrolment, all patients were screened for renal disorder by urine dipstick and urine analysis, kidney damage was suggested by the presence of proteinuria ≥1+, hematuria ≥5 RBC/high-power field or uninfectious leucocyturia ≥1+ without nitrite on two occasions 1 week apart. Calculation of eGFR was done by using the modification of diet in renal disease formula which is widely used formula in clinical practice.[10] In our study, if eGFR <60 ml/min/1.73 m² regarded as renal impairment. All patients with abnormal urine sediment underwent renal ultrasonography study to exclude local anatomical cause.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 24 (SPSS, IBM company, USA). The Chi-square test of association was used to compare the proportions. $P < 0.05$ was considered statistically significant.

Ethical consideration

The study was approved by the scientific and ethical committee of Kurdistan Board for Medical Specialties in accordance with the Helsinki's declaration guideline for the involvement of humans in research. All participants gave their written and informed consent.

Results

Out of 189 RA patients, 13 (6.8%) were dropped because of unwillingness or missing data. A total of 176 participants were analyzed, including 100 (56.8%) women, the mean age of the study subjects was 50 ± 10 years, 46 (26.1%) smokers, disease duration 8.3 ± 4.5 years, and BMI 28.7 ± 3.6 kg/m², renal impairment was detected in 20 patients (11.4%) with eGFR <60 mL/min/1.73 m² [Table 1].

The association between renal impairment and basic characteristics of the participants shows that, renal impairment was strongly associated with age >45 years, BMI ≥30, and longer disease duration >5 years ($P = 0.004$, 0.002, and 0.014, respectively), but not associated with gender, smoking status, and ESR level, ($P = 0.062$, 0.477, and 0.611, respectively). Almost all participants were on DMARDs, 112 (63.6%) of them were on one or more of the following DMARDs: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine, whereas 62 (35.2%) were on a biological agent (etanercept, adalimumab, or infliximab) in addition to a conventional DMARDs, 80 patients (45.5%) were on self-use or clinician prescription NSAIDs, the association of these medications with renal dysfunction were statistically not significant ($P = 0.229$, 0.261, and 0.137, respectively) [Table 2].

Proteinuria was detected in 18 participants (10.2%) and strongly associated with renal impairment ($P = 0.009$). Microscopic hematuria was recorded in 42 (23.9%) and

Table 1: Demographic characteristics of the participants

Parameters	Mean/*n*	SD/%
Age (years)	50.46	10.42
BMI (kg/m²)	28.72	3.64
Smoking	46	26.1
Creatinine (mg/dl)	0.9	0.28
ESR (mm/h)	50.69	28.54
eGFR (MDRD)	93.95	16.58
eGFR (<60)	49.4/20	8.42/11.4
Duration of RA (years)	8.3	4.5

eGFR in ml/min/1.73 m². BMI: Body mass index, eGFR: Estimated glomerular filtration rate, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, SD: Standard deviation, MDRD: Modification of diet in renal disease

uninfectious leucocyturia in 44 (25%) of the respondents, although their prevalence is a bit higher in patients with low eGFR but the association is statically not significant ($P = 0.074$ and 0.078, respectively) [Table 3].

The impact of RA medications on urine sediment shows no significant association between NSAIDs and DMARDs with proteinuria ($P = 0.949$ and 0.178, respectively). The prevalence of proteinuria was significantly less among patients using biological agent plus DMARDs $P = 0.009$. On the other hand, no statistically significant association detected between NSAIDs, DMARDs, and biological agent with hematuria ($P = 218$, 0.741 and 0.170, respectively) [Tables 4 and 5].

Discussion

RA is an autoimmune chronic systemic inflammatory disease involves the joints with extraarticular manifestations. Renal involvement in RA may be caused by disease process and the medications for control, it increases the morbidity and mortality by increasing the cardiovascular events.[11,12] In the current study, out of 176 RA patients, 11.4% of them had eGFR <60 ml/min/1.73 m². On comparing our results with related studies, it is a bit higher than that recorded in multicenter COMEDRA French study (8.8%),[13] but it is lower than that reported in recent study conducted in Pakistan (14.8%), in MATRIX study in UK (15%), in a nationwide database study in Japan, (18.5%) and in a study from Ethiopia (22.4%).[14-16] This variation could be explained by the exclusion criteria depended in this study, which excluded patients with comorbidities that might be an additional risk factor for kidney disease. The finding of the present study revealed that older age of participants was one of the strong predictors associated with renal insufficiency, this is similar to many other related studies.[13,14,16,17] This is possibly explained by the inverse relationship of advancing age and eGFR calculation in addition to the fact that with increasing age there is gradual decrease in nephrons number and concomitant decline in GFR. The present study shows that obesity (BMI ≥30) was significantly associated with renal impairment, this is consistent with Hickson *et al*. study[18] but inconsistent with several studies which used BMI >25 as cut off value for calculations.[12,14,19] Our results revealed that RA duration was significantly associated with renal dysfunction, similar to the data obtained in other studies[14,19] and inconsistent with COMEDRA study.[13] In the current study, there was no significant association of renal dysfunction with sex, smoking history, ESR level, or RA-related medications. Similarly, Couderc *et al*. revealed that there was no significant association between renal impairment and sex, disease activity (as assessed by DAS28-ESR), NSAIDs, and biological and conventional DMARDs.[7] Jima *et al*. found that Smoking and NSAIDs associated with renal impairment but sex and DMARDS not.[16] Two recently published study reported that the use of biological DMARDs may lower the risk of decreasing renal function in RA patients.[20,21] Proteinuria is associated with increased cardiovascular mortality in the general population[22] and in RA patients.[8] In the present study, proteinuria was associated significantly with renal impairment similar to Jima *et al*.'s study[16] and was less prevalent in patients using

Table 2: Association of studied parameters with impaired renal function

Variable	eGFR ≥60, *n* (%)	eGFR <60, *n* (%)	Total, *n* (%)	*P*
Age				
<45	64 (41)	2 (10)	66 (37.5)	0.004*
≥45	92 (59)	18 (90)	110 (62.5)	
Gender				
Male	71 (45.5)	5 (25)	76 (43.2)	0.062
Female	85 (54.5)	15 (75)	100 (56.8)	
BMI				
<30	93 (59.6)	5 (25)	98 (55.7)	0.002*
≥30	63 (41.4)	15 (75)	78 (44.3)	
Smoking				
Yes	42 (26.9)	4 (20)	46 (26.1)	0.477
No	114 (73.1)	16 (80)	130 (73.9)	
Duration of disease				
<5	65 (41.6)	3 (15)	68 (38.6)	0.014*
≥5	81 (58.4)	17 (85)	108 (61.4)	
ESR				
<60	102 (65.4)	12 (60)	114 (64.8)	0.611
≥60	54 (34.6)	8 (40)	62 (35.2)	
Medications DMARDs				
Yes	97 (62.2)	15 (75)	112 (63.6)	0.229
No	59 (37.8)	5 (25)	64 (36.4)	
bDMARDs				
Yes	54 (34.6)	8 (40)	62 (35.2)	0.261
No	102 (65.4)	12 (60)	114 (64.8)	
NSAIDs				
Yes	68 (43.6)	12 (60)	80 (45.5)	0.137
No	88 (56.4)	8 (40)	96 (54.5)	
Total	156 (100)	20 (100)	176 (100)	

*By Fisher's Exact test. eGFR (MDRD) mL/min/1.73 m. ESR: Erythrocyte sedimentation rate, DMARDs: Disease-modifying antirheumatic drugs, NSAIDs: Nonsteroidal anti-inflammatory drugs. bDMARDs: Biological agent plus conventional DMARDs, eGFR: Estimated glomerular filtration rate, BMI: Body mass index, MDRD: Modification of diet in renal disease

Table 3: Association of estimated glomerular filtration rate with urine sediments of participants

	eGFR ≥60, *n* (%)	eGFR <60, *n* (%)	Total, *n* (%)	*P*
Proteinuria				
Yes	10 (6.4)	8 (40)	18 (10.2)	0.009*
No	146 (93.6)	12 (60)	158 (89.8)	
Hematuria				
Yes	34 (21.8)	8 (40)	42 (23.9)	0.074
No	122 (78.2)	12 (60)	134 (76.1)	
Leucocyturia				
Yes	36 (23)	8 (40)	44 (25)	0.078
No	120 (77)	12 (60)	132 (75)	
Total	156 (100)	20 (100)	176 (100)	

*By fisher's exact test. eGFR (MDRD) mL/min/1.73 m. eGFR: Estimated glomerular filtration rate, MDRD: Modification of diet in renal disease

Table 4: The association of rheumatoid arthritis medications with proteinuria

	No proteinuria, *n* (%)	Proteinuria, *n* (%)	Total, *n* (%)	*P*
NSAIDs				
Yes	72 (45.6)	8 (44.5)	80 (45.5)	0.949
No	86 (54.4)	10 (55.5)	96 (54.5)	
DMARDs				
Yes	102 (64.5)	10 (55.5)	112 (63.6)	0.718
No	56 (35.5)	8 (44.5)	64 (36.4)	
bDMARDs				
Yes	50 (31.7)	12 (66.6)	62 (35.2)	0.009*
No	108 (68.3)	6 (33.4)	114 (64.8)	
Total	158 (100)	18 (100)	176 (100)	

*By fisher's exact test. DMARDs: Disease-modifying antirheumatic drugs, NSAIDs: Nonsteroidal anti-inflammatory drugs, bDMARDs: Biological agent plus conventional DMARDs

Table 5: The association of rheumatoid arthritis medications with hematuria

	No hematuria, *n* (%)	Hematuria, *n* (%)	Total, *n* (%)	*P*
NSAIDs				
Yes	56 (41.8)	24 (57.1)	80 (45.5)	0.218
No	78 (58.2)	18 (42.9)	96 (54.5)	
DMARDs				
Yes	84 (62.7)	28 (66.6)	112 (63.6)	0.741
No	50 (37.3)	14 (33.4)	64 (36.4)	
bDMARDs				
Yes	44 (32.8)	18 (42.9)	62 (35.2)	0.170
No	90 (67.2)	24 (57.1)	114 (64.8)	
Total	134 (100)	42 (100)	176 (100)	

*By Fisher's Exact test. DMARDs: Disease-modifying antirheumatic drugs, NSAIDs: Nonsteroidal anti-inflammatory drugs, bDMARDs: Biological agent plus conventional DMARDs

biological agents with DMARDs. Proteinuria, hematuria, and uninfectious leucocyturia were observed in 10.2%, 23.9%, and 25% of the study participants, respectively; our results is near to that reported in MATRIX study 16.2%, 17.2%, and 20.2% of the patients, respectively.[5] Mori *et al*. in a large cross-sectional study identified proteinuria in 8.1% (155 out of 1908 patients), and hematuria in 7.5% (143 out of 1908 patients), both were more prevalent in the renal dysfunction group.[19] Koseki *et al*. in a prospective study of renal disease with early RA, noted persistent proteinuria in 7% mostly drug-related (Gold and D-Penicillamine but not Methotrexate), and isolated hematuria in 17% which was associated with disease activity rather than treatment.[23]

Limitations of the study

First, it was a cross-sectional study, which cannot establish cause-effect relationship. Second sample size was small. However, it has few strong points, like it was the first study carried out on local population in Kurdistan, Iraq, about renal involvement in RA patients.

Conclusions

Renal disorder is common in RA patients. Regular monitoring of renal involvement by using eGFR and urinary dipstick is crucial, especially in elderly obese RA patients with a long duration of the disease and proteinuria. Early identification of renal disease can facilitate early intervention and achieve better management of RA patients.

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Conflicts of interest

There are no conflicts of interest.

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