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Renal function in patients with rheumatoid arthritis in Rafsanjan city in 2021

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Renal involvement is one of the extra-articular manifestations of rheumatoid arthritis (RA). The current study aims to investigate renal function and its associated factors in RA patients. This cross-sectional study included 443 RA patients who were referred to Rafsanjan's only rheumatology clinic in 2021. Disease Activity Score 28 (DAS28) index was used to determine disease activity. Blood levels of creatinine, C-Reactive Protein test (CRP), Erythrocyte Sedimentation Rate (ESR), and urine analysis were also determined. Renal failure was classified based on Estimated Glomerular Filtration Rate (eGFR). SPSS.20 one-way ANOVA, Kruskal-Wallis test, the Mann-Whitney U test, and Chi-square were used to analyze the data. Patiens' mean age was 53.99 ± 12.34, and 85.8% (380 people) of the participants were female. Ther were 147 (33.2%) patients without renal failure, 260 (58.7%) with mild renal failure, and 36 (8.1%) with moderate/severe failure. Men had a 3.059 higher risk of renal failure than women (P = 0.001). The probability of developing renal failure in patients increased by 1.047 times with each year of age (P < 0.001). As a chronic disease, RA can directly or through the use of disease medications and other risk factors, adversely affect other organs of the body, including the kidney. The current study's findings revealed a high prevalence of mild renal failure in these patients.

Keywords: Rheumatoid arthritis; Renal Failure; Creatinine; C-Reactive Protein; Erythrocyte sedimentation rate

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic systemic inflammatory diseases of the joints, resulting in joint destruction, deformation, or loss of function [1, 2]. The clinical symptoms of the disease include polyarthritis, inflammation of hand and knee joints, and extra-articular manifestations, such as rheumatoid nodules, pulmonary fibrosis, vasculitis, and serositis [2, 3]. This disease affects 2-3% of the population, with women being three times more affected than men [4]. A study in Tehran found that the prevalence of RA was 0.36%, with 0.57% in women and 0.14% in men [5]. It has been reported that the prevalence of this disease is six times higher in Iranian women than in men [6]. Epidemiological studies have found that various environmental, genetic, and immunological factors, as well as gender, age, pregnancy, smoking, obesity, infections, and improper

nutrition, all play a role in the occurrence of the disease [7 , 8].

Because RA has a variable disease course, 15-20% of patients have intermittent disease with periods of exacerbation and remission with a relatively good disease course [9]. In most cases, this disease has a hidden and gradual onset, accompanied by fatigue, anorexia, general weakness, muscle and bone pains, and, in rare cases, fever without an infectious cause [10, 11].

Disability is common and significant, so that people with RA become unable to perform all kinds of activities within a few years [12]. Joint symptoms, among the most common signs of the disease onset, usually appears gradually in several joints, particularly the hand, knee, and foot joints. These joints are symmetrically involved, resulting in joint damage if left untreated. If articular cartilage inflammation is not controlled, the groundwork for joint destruction and deformity is provided [11, 13].

Although RA is generally not a fatal disease, the complications associated with it can increase patient mortality [14, 15]. One of the extra-articular manifestations of this disease is renal involvement. Disease-modifying anti-rheumatic drugs (DMARDs), uncontrolled systemic inflammation, non-steroidal and anti-inflammatory drugs (NSAID) previously caused renal failure in these patients. However, using methotrexate and biological drugs, reduced NSAID consumption, and promotion of a targeted treatment strategy reduced the renal manifestations of patients [16]. Renal failure in RA patients is clinically significant because it not only limits primary disease management but also increases patient mortality. The mortality rate of RA patients with renal failure is significantly higher than patients with normal renal function [16]. Autopsy findings in RA patients shown that renal failure is the leading cause of death in 3-20% of cases [17]. Although previous studies in the general population have found that inflammation contributes to renal failure (18, 19), recent studies in RA patients have found conflicting results regarding renal involvement [19-22]. Therefore, renal involvement appears to be increasing in RA patients, and evidence suggests that renal failure is more common in these patients [18, 23]. The present study sought to investigate renal function

and its associated factors in RA patients.

Method

The present cross-sectional study included all RA patients referred to Rafsanjan's only rheumatology clinic in 2021. In this study, 443 patients were examined by census. All patients gave their informed consent to participate in the study. The inclusion criteria were a diagnosis of RA based on the criteria of American College of Rheumatology/European League against Rheumatism (ACR/EULAR 2010) [24] by a rheumatologist and at least one year history of the disease. A researcher-made checklist was used for data collection, which included variables of age, gender, education, marital status, occupation (Unemployed, employed), body mass index (BMI), duration of disease, type of used drug, underlying disease history (hypertension, diabetes, hyperlipidemia, ischemic heart and brain disease), history of smoking (active and passive), and opioid use, fasting blood glucose level, disease severity, Disease Activity Score 28 (DAS28) index, blood level of creatinine (Cr), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR) [25]. Urinalysis was performed on these patients to check for presence or absence of proteinuria on urine dipstick and hematuria (presence of > 3 red blood cells/high power microscopic field) [25]. The DAS28 index was used to determine the severity of RA. DAS28 is RA severity index based on the number of joints with swelling, the number of joints with local sensitivity, ESR, and patient's global estimate of status. The acceptable range of this index is 0 to 10. The DAS28 index value represents remission (less than/equal to 2.6), low (2.6 to 3.2), moderate (3.2 to 5.1), and severe disease activity (greater than/equal to 5.1) [26]. The following formula was used to classify renal failure based on Estimated Glomerular Filtration Rate (eGFR):

[eGFR (mL/min/1.73m2) = 186 (Serum. Cr in µmol/l × 0.011312) -1.154 × (age)-0.203 × (0.742 if female) × (1.212 if African/American Black)]

Normal renal function was defined as eGFR >90 ml/min/1.73 m2 (147 people), mild renal failure was defined as eGFR 60-89 ml/min/1.73 m^2 (260 people), and moderate/severe failure was defined as eGFR 5 ml/min/1. 3 m2 (36 people) [2].

The collected data were analyzed using SPSS20

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software. The results for the normal quantitative variables were reported in the three groups of patients without renal failure, patients with mild renal failure, and patients with moderate/severe renal failure in the form of mean ± standard deviation and one-way ANOVA test with Tukey's post hoc test. The quantitative variables with skewed distributions were reported as interquartile ranges (1st and 3rd quartiles) and the Kruskal-Wallis test, along with the Mann-Whitney U test. For qualitative variables in the form of number and percentages, Chi-square and Fisher's exact tests were used. The relationship between independent variables and renal failure in the patients was investigated using the proportional odds model for ordinal responses test. The P-value for the univariate analysis (which includes the variables of gender, age, education, smoking, history of diabetes, history of hypertension, history of high cholesterol, and consuming DMARD and biological medicine), was ≤0.10, and the variables were included in the multivariate model. For statistical analysis, SPSS/22 statistical software (IBM SPSS Inc., Chicago, IL, USA) and SAS/9.2 statistical package (SAS Institute Inc., Cary, NC, USA) were used. In all the tests, two-sided P-values and a significance level of 0.05 were considered.

Results

In this study, 443 RA patients were examined. Table 1 depicts the findings in relation to the patien's underlying variables. According to the eGFR index, renal function was normal in 147 (33.2%) patients, and mild and moderate/severe failure was observed in 260 (58.7%) and 36 (8.1%), respectively. Table 2 shows the laboratory indicators of RA patients based on the severity of their renal failure. The mean ESR (mm/hr) and frequency of positive were significantly higher in RA patients with moderate/severe renal failure when laboratory indicators were examined in three groups of patients with evidence of renal failure (Table 2). Table 3 reveals Proportional Odds Model predictors of renal failure in RA patients with ordinal responses. Input variables to the model included gender, age, education, smoking, historyof diabetes, history of hypertension, history of high cholesterol, and consuming DMARD and biological drugs. As the

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Discussion

RA is an inflammatory and chronic autoimmune disease affecting various tissues of the body and causes variety of adverse consequences, including joint destruction and patient death. Renal disorders and diseases have also been reported in patients with RA, resulting in proteinuria, hematuria, and renal dysfunction in some RA patients [28, 29]. Renal failure not only affects RA management, but it also increases the risk of death in these patients [30]. According to the findings of this study, 58.7% of RA patients had mild and 8.1% had moderate/severe renal failure (eGFR < 59 ml/min/1.73 m2). Despite lack of a control group in our study, compared to other studies on the prevalence of renal failure in the Iranian normal population, the frequency of CKD in RA patients was not higher. A meta-analysis of the prevalence of CKD in the Iranian population reported a 15.1% prevalence (eGFR < (eGFR < 59 ml/min/1.73 m²) for people of all

Table 1: Frequency distribution of underlying variables and disease severity in patients with RA

Variables	Total (n=443)	Moderate/severe renal failure (n-36)	Mild renal failure (n = 260)	No renal failure (n = 147)	P-value
Age[a], year	53.99 ± 12.34	47.3 ± 12.3	52.6 ± 12.2	58.1 ± 11.4	< 0.001
Female[b] number (%)	380 (85.8)	25 (69.4)	219 (84.2)	136 (92.5)	< 0.001
Marriage[b] number (%)	407 (91.9)	33 (91.7)	239 (91.9)	135 (91.8)	0.995
Education level[b]					0.014
Illiterate, number (%)	83(18.7)	3(8.3)	42(16.2)	38(25.9)	
Under diploma, number (%)	186 (42)	12 (33.3)	111 (42.7)	63 (42.9)	
Diploma, number (%)	124 (28)	14 (3809)	73 (28.1)	37 (25.2)	
Academic degree, number (%)	50 (11.3)	7 (19.4)	34 (13.1)	9 (6.1)	
Employee[b], number (%)	281 (63.4)	18 (50)	166 (63.8)	97 (66)	0.153
Active smoker, number (%)	38 (8.6)	6 (16.7)	25 (9.6)	7 (4.8)	0.015
Passive smoker, number (%)	149 (33.6)	9 (25)	92 (35.4)	48 (32.7)	0.444
Opioid use, number (%)	29 (6.5)	3 (8.3)	17 (6.5)	9 (6.1)	0.681
BMI[b]					0.166
Underweight	9 (2)	2 (5.6)	6 (2.3)	1 (0.7)	
Normal	80 (18.1)	11 (30.6)	45 (17.3)	24 (16.3)	
Overweight	160 (36.1)	12 (33.3)	96 (36.9)	52 (35.4)	
Obese	194 (43.8)	11 (30.6)	113 (43.5)	70 (47.6)	
Duration of disease[c], years	4 (2-7)	3.5 (2-7)	4 (2-7.75)	5 (3-7)	0.655
Disease severity[b] (DAS28)					0.657
Mild, number (%)	97 (21.9)	5 (13.9)	61 (23.5)	31 (21.1)	
Moderate, number (%) Severe, number (%)	341 (77) 5 (1.1)	31 (86.1) 0	195 (75) 4 (1.5)	115 (78.2) 1 (0.7)	
Medications[b]					
Glucocorticoid	401 (90.5)	34 (94.4)	238 (91.5)	129 (87.8)	0.134
Methotrexate, number (%)	346 (78.1)	29 (80.6)	200 (76.9)	117 (79.6)	0.768
DMARDs, number (%)	223 (50.3)	15 (41.7)	143 (55)	65 (44.2)	0.062
Biologicals, number (%)	61 (13.8)	1 (2.8)	34 (13.1)	26 (17.7)	0.024
NSAIDs, number (%)	89 (20.1)	6 (16.7)	47 (18.1)	36 (24.5)0.123	0.123
Underlying disease[b]					
Diabetes, number (%)	74 (16.7)	7 (19.4)	35 (13.5)	32 (21.8)	0.088
High cholesterol, number (%)	214 (48.3)	12 (33.3)	117 (45)	85 (57.8)	0.002
Hypertension, number (%)	159 (35.9)	10(27.8)	77 (29.6)	72 (49)	<0.001
Ischemic heart, number (%)	3 (0.7)	0	3 (1.2)	0	0.656
Stroke, number (%)	4 (0.9)	0	2 (0.8)	2 (1.4)	0.731

[a] Values are in the form of mean ± standard deviation, ANOVA test and significance level is 0.05.

[b] Values are in the form of number (percentage), Chi-square test and significance level is 0.05.

[c] Values are in the form of median (1st quartile and 3rd quartile), Kruskal-Wallis test and significance level is 0.05.

all ages and a 24.3% prevalence for people over 40 [31]. Saisho et al. showed that the prevalence of chronic kidney disease (CKD) in RA patients based on eGFR was 25.4% in G1 stage, 55.9% in G2 stage, 17.5% in G3 stage, 0.8% in G4 stage, and 2.2 0% in the G5 stage [32].

Table 2: Distribution of laboratory indicators in patients with RA

Variable	Moderate/severe renal failure (n = 36)	Mild renal failure (n = 260)	No renal failure (n =147)	P-value
Fasting blood sugar[a] (mg/dl)	92.5 (85.75-112)	96 (89-107)	92 (88-104)	0.589
ESR[a](mm/hr)	33 (20-37)	19 (10-30)	9 (5.23)	0.004
CRP[b] (positive)	13 (36.1)	130 (50)	63 (42.9)	0.163
RF[b] (positive)	16 (44.4)	142 (54.6)	94 (63.9)	0.055
Proteinuria[b]	3 (2)	7 (2.7)	1 (2.8)	0.915
Hematuria[b]	16 (10.9)	25 (9.6)	3 (8.3)	0.869

[a]: Values are in the form of median (1st quartile and 3rd quartile), Kruskal-Wallis test and significance level is 0.05.

[b]: Values are in the form of number (percentage), Chi-square test and significance level is 0.05.

Couderc et al. reported a prevalence of CKD of 8.8% [33] and Mori et al. reported 33.8% [33]. In the study of Kochi et al., 16% of RA patients developed CKD during 89 months of follow-up. Furthermore, the simultaneous presence of inflammation and CKD in the patients resulted in a higher risk of cardiovascular diseases [22].

The results of different studies have indicated the prevalence of renal dysfunction in different studies and regions. The noteworthy point in most studies is that unlike our study, the frequency of renal disorders in patients with RA is higher than the general population. It has been reported that the higher prevalence of CKD in RA patients was

Table 3: Predictive factors of renal failure in RA patients based on Proportional Odds Model for ordinal responses

Variable	Unadjusted			Adjusted		
	OR*	95% CI for OR	P-value	OR*	95% CI for OR	P-value
Gender Male compared to female	2.788	1.585-4.903	0.004	3.059	1.733-5.401	0.0001
Age	1.046	1.029-1.062	< 0.001	1.047	1.031-1.064	< 0.001

* Input variables to the model include gender, age, education, smoking, history of diabetes, history of high blood pressure, history of high cholesterol, use of DMARD and biological drugs.

OR, Odds Ratio; CI, Confidence Interval

related to several conditions, such as secondary amyloidosis, glomerulonephritis or the use of nephrotoxic drugs, and a continuous increase in CRP for at least 6 months [18, 23, 35, 36]. However, the specific causes of CKD are generally unknown among most patients, and it is important to determine its[risk factors [18].

The study results also indicate that RA patients with moderate/severe renal failure had a median ESR of 33 mm/hr, proteinuria in 2.5%, hematuria in 9.9% and positive rheumatoid factor (RF) in 13.3%. Examining the relationship between the mentioned indicators and renal function indicated the significant difference

in the mean serum level of ESR in patients with renal dysfunction, so that the serum level of ESR was higher in patients with moderate/severe renal failure. Other indicators did not have statistically significant differences. In the study by Fayed et al., there was no significant difference between proteinuria in the form of nephrotic syndrome, persistent proteinuria, and recurrent hematuria, in RA patients [16]. Mori et al. reported that although albuminuria was observed in 1.8% of patients and hematuria in 7.5% of patients with RA, the results did not show any significant difference [34]. The results of the study by Hickson et al. indicated that the ESR level was higher in RA patients, which was significantly associated with increased risk of kidney diseases [20]. Although ESR is used as an index to evaluate inflammation, indices, such as CRP, serum amyloid A proteins, and procalcitonin have higher sensitivity and increase more than 100 times in some patients with acute or chronic inflammatory disorders. During an inflammatory reaction, ESR is affected by various factors; however, the sedimentation rate is often significantly influenced by many factors other than the acute phase reaction [37]. High ESR value in RA patients has been associated with higher joint destruction [38] and on the other hand, high ESR is related to special activity of organs, such as kidney and renal failure [39]. However, the ESR level is higher in patients with CKD, and it is necessary to compare with the healthy group and conduct studies with a more precise design to prove this relationship.

Another finding of the study was related to underlying diseases in RA patients, so that most patients with moderate/severe renal failure and mild renal failure had at least one underlying disease. High cholesterol and hypertension also had a statistically significant difference in the three groups, indicating that their frequency was higher in patients with moderate/severe renal failure. One of the most important underlying diseases related to renal failure in RA patients is hypertension, which is related to the prevalence of renal disorders in these patients [33]. Another underlying disease that is significantly associated with renal dysfunction in RA patients is cardiovascular disease and hypertension and

lipid profile disorder are considered its risk factors. Meanwhile, RA patients who suffer from renal failure have a higher risk of developing cardiovascular diseases [20, 22].

In the present study, among all the studied drugs, only a statistically significant difference was observed between the use of biological drugs and the type of renal function in the three groups, so that in RA patients with renal failure, there was low frequency of using biological drugs. The results of the study by Onishi et al. showed that the effectiveness of biological drugs in preventing the decrease in eGFR and thus reducing the risk of CKD is significantly higher than other drugs used in the treatment of RA [42]. In a study on hydroxychloroquine (HCQ), CKD was reported in 3.96% of users and 8.59% of patients who did not use it, indicating a lower frequency of CKD in users of this drug [40]. The study by Nazir et al. reported the positive effect of HCQ treatment on reducing renal disorders related to RA [41]. HCQ treatment was not only effective in reducing disease progression in RA patients, but also enhanced the effects of methotrexate in the treatment of RA [41]. Therefore, the accurate selection of drugs in RA patients is very important to reduce the complications of the disease, including renal failure [25]. The results of the present study also showed that male gender and increasing age are factors that increase the risk of renal failure in RA patients. Onishi et al noted that although RA patients with higher disease severity (based on DAS28) had better baseline eGFR, over time, the course of eGFR significantly showed an unfavorable trend. Moreover, increasing age was significantly associated with progressive eGFR reduction [42]. The results of Couderc's study showed that this relationship was significant for age, but not for gender, disease duration, and disease activity [33]. In another study, disease severity based on DAS28 and duration of RA were reported as risk factors for CKD, but no significant difference was observed based on age and gender [43].

The increase in CKD can occur due to the higher occurrence of indicators, such as drug-induced proteinuria and hematuria in older patients [44]. Helin et al. based on biopsies of all RA patients, mentioned that the cause of this increase might be due to anti-rheumatic treatment

or RA disease itself [35]. For instance, NSAIDs can cause worsening kidney function, which is especially common in older patients. cyclosporine is another potentially nephrotoxic DMARD that causes constriction of afferent and efferent glomerular arterioles, resulting in a decrease in renal blood flow and eGFR, and its side effects increase with age. Long-term use of cyclosporine can cause obliterative arterio-pathy, ischemic scar, tubular atrophy, and progressive CKD [45].

Among the limitations of this study the lack of a control group and descriptive design of the study also reduces the accuracy of the results to express the cause and effect relationship. But the collection of information from only the rheumatology clinic of Rafsanjan city, which possible the generalizing the results to the entire population.

Conclusion

RA, as a chronic disease, can cause adverse effects directly or through the use of disease medications and other risk factors on other organs of the body, including the kidney. The results of the present study indicated the high prevalence of mild renal failure but not CKD in these patients. An increase in inflammatory indicators, such as ESR, underlying diseases, such as high cholesterol and hypertension, male gender, and increasing age were among the factors affecting renal failure in RA patients.

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Conflict of interest

The authors declare no conflict of interest.

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