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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Histofunctional status of kidney in patients with rheumatoid arthritis

Romatoid Artrit'li hastalarda böbreğin histopatolojik ve fonksiyonel durumu

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ABSTRACT

Objectives: The aim of this study was to observe the effects of duration and severity of disease on renal functions and histopathology in patients with rheumatoid arthritis (RA).

Material and methods: The study included 50 patients of RA, who were divided into two groups of 25 patients each. Disease severity was assessed by Disability Activity Score (DAS). The renal parameters i.e., urine complete examination, blood urea, serum creatinine and creatinine clearance were estimated at enrolment. Percutaneous renal biopsy was performed in patients having active urinary sediment, haematuria and/or proteinuria more than 300 mg/day and serum creatinine more than 1.5 mg/ml.

Results: Group I patients had duration of disease between 2-5 years and in Group II the duration was more than 5 years. Urine abnormalities were documented in 28% RA patients and 12% patients had isolated hematuria, 10% patients presented with isolated proteinurea and combined haematuria and proteinurea was present in 6% patients.14% patients presented with raised creatinine(>1.5mg/ml). Renal biopsy was performed in 20% of patients which showed mesangial glomerulonephritis, membranous glomerulonephritis, secondary amyloidosis and interstitial nephritis. In group I severe DAS score was present in 17% of the patient having urinary abnormality, however 20% patients showed histopathological findings. In group II 63% of patients with severe DAS score had urinary abnormality, 83% showed raised serum creatinine and 60% had histopathological abnormalities indicating severe DAS score and increased duration of disease was associated with significant effects on histofunctional status of kidney.

Conclusion: There was a significant increase in renal dysfunction with duration and severity of disease in rheumatoid arthritis.

Key words: Rheumatoid arthritis, renal functions, histopathology, haematuria, proteinuria

ÖZET

Amaç: Bu çalışmanın amacı romatoid artritte romatoid artritli (RA) hastalarda hastalık şiddeti ve süresinin böbrek fonksiyonları ve histopatoloji üzerine etkilerini gözlemektir.

Gereç ve yöntem: Çalışmaya her biri 25'er hasta içeren iki gruptan oluşan toplam 50 hasta alındı. Hastalık şiddeti sakatlık aktivite skoru (SAS) ile değerlendirildi. Tam idrar tetkiki, serum üre ve kretinini ve kreatinin klirensi gibi böbrek değişkenleri hastaneye ilk başvuruda kaydedildi. Aktif idrar sediment bulunan, hematuria ve/veya 300 mg/gün'den fazla proteinürisi bulunan ve serum kreatinini 1.5 mg/dl üzerinde olan hastalara perkutan böbrek biyopsisi uygulandı.

Bulgular: Grup I hastalarda hastalık süresi 2-5 yıl arasında, Grup II'de 5 yıldan uzun süreli idi. Romatoid artritli hastaların %28'inde idrar anormallikleri saptandı, bunların %12'sinde izole hematüri, %10'unda izole proteinüri, %6'sında ise hematüri ve proteinüri birlikte görüldü. Hastaların %14'ünde yüksek serum kreatinin değeri (>1.5 mg/dl) saptandı. Hastaların %20'sine böbrek biyopsisi uygulandı ve biyopsi sonucunda histopatolojik olarak mezanjiyal glomerülonefrit, memebranöz glomerülonefrit, sekonder amiloidoz ve interstisyel nefrit bulundu. Grup II'de ağır SAS bulunan hastaların %63'ünde idrar anormallikleri saptanırken, %83'ünde artmış serum kreatinin ve %60'ında ağır histopatolojik anormallikler saptandı. Bu durum ileri düzeyde SAS ve uzamış hastalık süresinin böbrek histofonksiyonel durumu üzerinde önemli etkilerle birlikteliğini göstermekteydi.

Sonuç: Romatoid artritte hastalık süresi ve ağırlığına paralel olarak renal fonksiyon bozukluğunda bir artış olduğu gözlendi.

Anahtar kelimeler: Romatoid artrit, böbrek fonksiyonları, hematüri, proteinüri

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INTRODUCTION

Renal disease is a well recognised cause of ill health and death in patients with Rheumatoid arthritis (RA). Two broad categories of renal involvement occur in such patients: The first being attributed to the disease itself i.e. secondary amyloidosis, mesangial glomerulonephritis, membranous glomerulonephritis, renal vasculitis and interstitial nephritis. Second is due to nephrotoxicity from drugs used for treatment of arthritis i.e. Non-steroidal anti-inflammatory drugs (NSAID's) and Disease modifying anti rheumatic drugs (DMARD's) especially gold and penicillamine.[1] The secondary amyloidosis may present with proteinuria, nephrotic syndrome or renal impairment. The various types of glomerulonephritis may present with isolated hematuria, isolated proteinuria or combined hematuria and proteinuria.

The etiopathogenesis of renal involvement in RA patients is less clearly understood; however a high prevalence of renal impairment with evidence of reduced glomerular filtration rate (GFR) and tubular dysfunction in RA patients is well documented.[2] When renal involvement in connective tissue disease is described, traditionally the focus has been on systemic lupus erythematosis, however, renal involvement in RA continues to be one of the important causes of mortality next only to cardiovascular disease and infections. [3]

The diagnostic importance of early detection and etiopathogenesis of renal involvement in RA patients is self explanatory, as approach towards the management will differ with each. Therefore, the present study has been planned to study the histofunctional status of kidney in patients of Rheumatoid arthritis.

MATERIALS AND METHODS

The present prospective cross sectional study was conducted on fifty adult patients of RA diagnosed as per the American College of Rheumatology 1987 revised criteria4 from Rheumatology and Medicine department of Pt.BD Sharma PGIMS, Rohtak (India) who were already on follow up and receiving treatment.

Patients with chronic systemic diseases like chronic liver disease, congestive cardiac failure, diabetes mellitus and hypertension were excluded. Similarly, moribund patients and patients with any other disease causing renal dysfunction were also excluded from the study group.

Written informed consent was taken prior to enrolment in the study from each patient. All patients were subjected to detailed history, clinical examination and investigations with special reference to renal functions. The patients were divided into two groups (I and II) of twenty five patients each depending upon duration of RA.

Group I – patients having RA of more than 2 years but less than 5 years duration (2-5 yrs).

Group II – patients having RA of more than 5 years duration.

Baseline values of Blood urea, Serum creatinine, urine complete examination and creatinine clearance were estimated in all patients, irrespective of group.

The proteinuria was assessed by Ames dipstick test and 1+ or greater (albumin >250 mg/l) was interpreted as abnormal. Hematuria was defined as the presence of ≥5 red blood cells per high power field under microscopic examination. The creatinine clearance was measured by Cock-croft Gault formula.[5] Specific investigation i.e., percutaneous renal biopsy was performed after obtaining an informed consent in patients having active urinary sediments, haematuria and/or proteinuria more than 300 mg/day and serum creatinine >1.5 mg % irrespective of the group. Renal biopsy specimen were subjected to light microscopy using hemotoxylin & eosin, periodic acid, congo red Schiff, gomori methnamine silver stains and immunoflorescence studies. All patients included in the study were evaluated for their disease activity by modified DAS scores (disability activity score).[6]

Calculation of DAS 28 involves four variables and was calculated as per following equation:

DAS 28 = 0.50 TJC* + 0.28 SJC* + 0.70 Log ESR*** + GH 0.014**** where

* TJC is tender joint count

** SJC is swollen joint count

*** Log erythrocyte sediment rate

**** GH is global health status of patients as assessed by visual analogue scale.

DAS score involves 28 specific joints including shoulder, elbow, wrist, MCP, PIP and knee joints.

Based on DAS, patients score of >5.1 indicate high disease activity, score of <3.2 indicate low disease activity and score of <2.6 indicates patient in remission

Statistical Analysis

The data obtained was subjected to standard statistical analysis. The continuous variables were recorded as Mean+1SD. Students t test and chi square tests were used for comparison of various values between two groups.

RESULTS

The study included fifty patients, 25 in each group. Majority of patients were female (84%) (Table 1). The age range of the patients were 23-58 years in group I (43.4±9.2) and 34-68 years in group II (51.04 ±10.7). The mean hemoglobin in group I was 10.2 ± 1.2 gm % while in group II it was 9.01± 1.36 gm % which was statistically significant (<0.001). Anemia was present in both groups but more common in group II. The mean value of blood urea in group I was 29.00±14.41mg% and in group II was 46.04±27.90mg%. The mean value of serum creatinine in group I was 0.94±0.68mg% and in group II it was 1.90±2.27mg%. There was statistically significant difference in values of blood urea and serum creatinine between two groups. The mean value of GFR in group I was 104.81±27.04ml/min and in group II was 90.31±46.77ml/min. There was statistically significant difference in GFR values between two groups (Table 2). Renal dysfunction i.e., increased blood urea, increased serum creatinine and decreased creatinine clearance was present in 4% of patients in group I and 24% of patients in group II, which indicated significant increase in renal dysfunctions in group II patients who had increased duration of disease (Table 3).

Isolated haematuria was present in 12% of patients each in group I and II. Similarly, isolated proteinuria was present in 8% of patients in group I and 12 % of patients in group II, whereas combined haematuria and proteinuria was present in 4 % of patients in group I and 8% of the patients in Group II (Table 4).

Twenty four hour urinary protein more than 2.5 g/day was present in 16% of patients in group II as compared to 8% of patients in group I. Proteinuria in the range of 0.3 to 2.5gms/day was present in 24% of patients in group II, as compared to 8% of patients in group I, indicating that more patients had significant proteinuria in group II, correlating it with duration of disease (Table5).

Three patients presented with isolated haematuria in group I out of which two consented for renal biopsy, both patients had mesangial glomerulonephritis. Among two patients who presented with isolated proteinuria, one showed membranous glomerulonephritis and the other had FSGS. One patient who had combined haematuria and proteinuria was having chronic interstitial nephritis.

In group II, three patients presented with isolated haematuria, one patient who consented for biopsy showed mesangial glomerulonephritis. Out of three patients who presented with isolated proteinuria in group II, two patients had amyloidosis, while one patient had membranous glomerulonephritis. One patient who was having both haematuria and proteinuria in group II had chronic interstitial nephritis. Therefore, all the patients having active urinary sediment showed histopathological changes on renal biopsy (Table 4).

The mean DAS was 3.76±0.69 in group I and 4.26±0.89 in group II. The comparison of DAS between two groups was statistically significant (>Table 2). Severe DAS score was more apparent in patients with deranged renal functions. In group I, severe DAS score was present in 17% of patients with urinary abnormalities and 20% of patients showing histopathological findings. While in group II, severe DAS score was present in 63% of patients with urinary abnormalities and 60% of patients with histopathological abnormality, thus indicating that severe DAS score was associated with significant effect on histofunctional status of kidney.($p<0.05$) (Table 6).

Table 1. Sex Distribution

Group	Male	Female	M : F ratio
Group I (n=25)	5	20	1 : 4
Group II (n=25)	3	22	1 : 7.3

Table 2. Biochemical parameters/renal parameters at baseline

Parameters	Group I (Mean±SD)	Group II (Mean±SD)	p value (unpaired)
Hemoglobin (gm%)	10.20±1.17	9.01±1.36	<0.001
Blood urea (mg%)	29.0±14.4	46.0±27.9	<0.01
S. Creatinine (mg%)	0.94±0.68	1.90±2.27	<0.05
Urine Output (ml/day)	1872±124	1730±432	NS
24 hour urine protein (g/l)	0.21±0.38	0.66±1.26	NS
24 hour urine creatinine (mg%)	84.92±11.19	76.96±15.92	<0.05
Creatinine clearance (ml/min)	104.8±27.0	90.3±46.8	<0.001
DAS *	3.76±0.69	4.26±0.89	<0.05

* Disability activity score. NS: Not significant

Table 3. Renal parameters

	Group I (n=25)		Group II (n=25)		Total (n=50)	
Parameters	n	%	n	%	n	%
Blood urea (>40mg%)	1	4	6	24	7	14
Serum creatinine (>1.5mg%)	1	4	6	24	7	14

Table 4. Clinico-histopathological correlation

Urinary abnormalities	Group II (n=25)			Group II (n=25)		
	n	Biopsy performed	Renal lesion	n	Biopsy performed	Renal lesions
Isolated haematuria	3(12%)	2	MsGN (2)	3(12%)	1	MsGN (1)
Isolated proteinuria	2(8%)	2	MnGN (1) FSGS(1)	3(12%)	3	MnGN (1) Secondary amyloidosis (2)
Haematuria and proteinuria	1(4%)	1	CIN (1)	2(8%)	1	CIN (1)

MsGN, mesangial glomerulonephritis; MnGN, membranous glomerulonephritis;FSGS , focal segmental glomerulosclerosis; CIN, chronic interstitial nephritis.

Table 5. Twenty-four hour urinary parameters

Parameters	Group I (n=25)		Group II (n=25)		Total (n=50)	
	n	%	n	%	n	%
Total proteinuria (0.3 to 2.5gm/day)	2	8	6	24	8	16
Total proteinuria (>2.5gm/day)	2	8	4	16	6	12
GFR <90ml/min	1	4	6	24	7	14

Table 6. Renal parameters with DAS score

	Group I (n=25)			Group I (n=25)			a
	n	severe DAS	%	n	severe DAS	%	P value
Urine abnormalities	6	1	17	8	5	63	<0.05
Increased serum creatinine (>1.5mg%)	1	1	100	6	5	83	>0.05
Histopathological findings	5	1	20	5	3	60	<0.05

DISCUSSION

Renal involvement in connective tissue diseases like systemic lupus erythematosis (SLE) is well recognised. Affection of kidney in RA is more or less overlooked and mainly attributed to drugs viz. Non steroidal anti inflammatory drugs (NSAIDs) and Disease modifying anti rheumatic drugs (DMARD's) like gold and d-penicillamine. Clinical manifestations of renal involvement in RA have been commonly attributed to secondary amyloidosis, usually associated with long time disease process.[7]

There is enough evidence that both functional abnormalities and histopathological lesions that may be attributed to disease itself do occur in RA patients.[8-10] Boers et al classified renal disease into three categories- those due to RA and its complications, those related to drug therapy and a third category, RA nephropathy due to disease itself.[11] There is high prevalence of renal impairment with evidence of reduced glomerular filtration rate (GFR) and tubular function in RA patients. These patients are at risk of developing renal complications and proteinuria which increases mortality rate.[12-14] In practice, renal involvement usually remains unnoticed for long period in a reversible subclinical stage and should therefore be detected as early as possible.[11,15]

In our study we observed that renal abnormalities were quite prevalent in RA patients and there was significant increase of renal derangement with duration of disease and severity of disease activity. 28% of patients in the present study showed urine abnormalities. Among them, isolated hematuria was persistent between groups whereas, isolated proteinuria and combined hematuria and proteinuria were more common in group II patients. The baseline renal parameters i.e. hemoglobin, blood urea and serum creatinine were significantly deranged in group II than in group I patients, thus suggesting that impairment of renal functions in the present study increased with duration of disease. Similar finding were observed by Pederson et al who studied 65 patients with RA for microalbuminuria and found that microalbuminuria was present in 27% of patients of RA, as against 7.8% of controls. A significant relation was noted between urinary albumin to creatinine ratio and CRP with the duration of disease.[16] Our findings are consistent with Sihvorien et al who studied 604 patients of RA and found isolated hematuria in 54 patients (8.9%), isolated proteinuria in 27 patients (4.5%) and combined hematuria and proteinuria in 7 patients (1.2%).[17]

Similar findings were observed by Karstila et al who assessed the frequency of abnormal clinical renal findings in a population of 103 RA patients. In this study 9% patients had isolated hematuria, 5% isolated proteinuria and 1% combined proteinuria and hematuria.[18] Koseki et al also studied 235 patients with early RA. They found 40 patients with hematuria and none had proteinuria. After 42 months of follow up persistent hematuria was found in 43 patients (18%) and persistent proteinuria in 17 patients (7%),[19] thus signifying the importance of regular monitoring of renal functions in RA patients. These findings are in agreement with the present study.

In the present study, renal biopsy was performed in 20% of patients who had renal abnormalities and consented for biopsy. The mesangial glomerulonephritis, characterized by mild mesangial hypercellularity with or without a slight increase in mesangial matrix & deposition of immunoglobulin and/or complement components, was more common in group I patients, suggesting that it develops early in RA patients who present with isolated hematuria. These findings were similar to findings of Korpela et al. who found significant correlation between intensity of IgA deposits and levels of IgM class rheumatoid factor.[20] These findings emphasize that mesangial glomerulonephritis is related to basic rheumatoid disease and should be regarded as an extra articular manifestation of RA.

Membranous glomerulonephritis, diagnosed by histopathological examination showing epimembranous spikes and granular subepithelial deposits, predominantly of IgG, was seen in one patient each in the two groups and both patients had isolated hematuria. The most common cause of membranous nephropathy in patients with RA was considered to be gold or penicillamine therapy in earlier days, however, many studies now highlight occurrence of membranous nephropathy even in patients of RA not been treated with gold or penicillamine.[21,22] Secondary amyloidosis was present only in group II patients suggesting that secondary amyloidosis might occur with long duration of disease. Chronic interstitial nephritis was present in one patient each in the two groups. Our findings are consistent with Nakano et

al who studied renal biopsy in 158 RA patients with renal abnormalities. They found mesangial GN in 54 patients, membranous GN in 49 and secondary amyloidosis in 30 patients.[23] Helin et al also noted mesangial GN more commonly (40%) than amyloidosis (33%) and membranous GN (19%) in patients with rheumatoid arthritis.[24] Korpela et al evaluated 1018 patients of RA for presence of isolated hematuria and histopathological changes in them. They reported mesangial glomerulopathy was the most common renal biopsy finding in RA patients with isolated hematuria.[20]

Boers et al studied 132 biopsies of RA patients with renal abnormalities and/or renal dysfunctions and they found secondary amyloidosis occurring with long duration of disease which was accompanied by proteinuria and uremia.[11]

We also tried to correlate renal dysfunction with severity of DAS score. The mean DAS score value was significantly higher in group II patients than in group I. In the present study,the RA patients with urine abnormalities and histopathological findings showed severe DAS score, thus suggesting that severity of DAS increased with duration of disease and renal involvement was more common in RA patients with severe DAS score.

The clinicohistopathological correlation of renal involvement in RA patients is less clearly understood and without doubt heterogenous. Secondary amyloidosis results from deposition of fibril containing AA protein which is antigenetically related to serum amyloid A(SAA) protein. SAA protein is increased up to 10000fold by inflammatory stimuli in RA.[7] Similarly there is a striking association of IgM rheumatoid factor with mesangial glomerulonephritis. There occurs a functional response of renal mesangium to remove IgM rheumatoid factor immunoglobulin G complex which leads to mesangial lesions.[20]

The present observations, albeit with limitation of small sample size, reveal that renal functions were significantly deranged in patients of rheumatoid arthritis, which may remain unnoticed at subclinical level if renal parameters are not monitored at regular basis. Although various biomarkers like urinary alfa-1 microglobulin estimation, urinary n-acetly glycosaminidase (NAG) and cystatin-c levels for glomerular and/or tubular proteinuria and GFR estimation are available, histopathology remains the gold standard to diagnose RA nephropathy.[15] Therefore the observations of the present study reveals that showed that RA patients should be routinely subjected to renal function tests and if required, renal biopsy may be considered in patients having urinary abnormalities and/or renal dysfunction to understand the histofunctional status of kidney. This approach will further help in dose modification of DMARD's and various other drugs used for the treatment of rheumatoid arthritis in this group of patients.

REFERENCES

1. Adu D, Amery P. The patient with rheumatoid arthritis, mixed connective tissue disease, or polymyosis: Oxford Textbook of clinical nephrology, 2nd ed. Oxford University Press: Davison AM, Camison S, Grunfeld JP, Ponticelli C, Litz E. Wincarls CG,1998; II: 975-85
2. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Block DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994; 4(3): 481-94
3. Murtru O, Laasko M, Isomaki H, Koota K.Ten year mortality and cause of death in patients with rheumatoid arthritis. Br Med J 1985; 290(11): 1797-9
4. Arnett FC. The American rheumatism association 1987 revised criteria for the classification of RA. Arthritis Rheum 1988; 31(3): 315-20.
5. Cockeroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
6. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38(1):44–8.
7. Cohen AS. Amyloidosis in arthritis and allied conditions: Arthritis and allied conditions, Philadelphia: DJ, Carty Mc, 1989: 1275-93.
8. Boers M, Croonen AM, Dijkonans BA, Breedveld FC. Renal findings in rheumatoid arthritis: clinical aspects of 132 necropsies. Ann Rheum Dis 1987; 46(4): 658-63.
9. Yoshida K, Morozumi K, Sunganuma T, Aoki J. Clinicopathological study of nephropathy in patients with rheumatoid arthritis. Rheumatoid 1991; 31(1): 14-21.
10. Braun A, Zeier M. Rheumatoid arthritis and the kidney. Uneasy companions. Nephron Clic Prac 2004; 96(1): 105-6
11. Boers M. Renal disorders in rheumatoid arthritis. Semin Arthritis Rhem 1990; 20(1): 57-68.
12. Dutchie JJ, Brown PE, Truclove LH, Baragar FD, Lawrie AJ. Course and prognosis in rheumatoid arthritis. A further report. Ann Rheum Dis 1964; 23(2): 193-204.
13. Jacobsson LTH, Knowler WC, Pillemer S. Rheumatoid arthritis and mortality. Arthritis Rheum 1993; 36(9): 1045-53.

14. Nadkar MY, Londhey VA. Investigating kidney. Involvement in rheumatoid arthritis. JAPI 2004; 52(3): 447-8.
15. Karstila K, Harmoinen A, Lentimaki T, Korpela M, Mustonen T, Saha H. Measurement of kidney function in patients with rheumatoid arthritis: Plasma cystatin C versus Cr-EDTA clearance. Nephron Clin Prac 2008:25(1): 13-8.
16. Pederson LM, Nordin H, Svensson B, Biddla H. Microalbuminuria in patients with rheumatoid arthritis. Ann Rheumatic Dis 1995; 54(2): 189-92.
17. Sihvonen S, Korpela M, Mustonen J, Laippala P, Pasternack A. Renal disease as a predictor of increased mortality among patients with rheumatoid arthritis. Nephron Clin Pract 2004; 96(1): 107-14.
18. Karstila K, Korpela M, Shivonen S, Muslonen J. Prognosis of clinical renal disease and incidence of new renal findings in patients with rheumatoid arthritis; follow up of a population based study. Clin rhematoi 2007; 26: 2089-95.
19. Koseki Y, Terai C, Moriguchi M, Uesato M, Kamatani N. A prospective study of renal disease in patients with early rheumatoid arthritis. Ann Rheum Dis 2001; 60(2): 327-31.
20. Korpela M, Mustonen J, Teppo AM, Helin H, Pasternack A. Mesangial glomerulonephritis as an extra-articular manifestation of rheumatoid arthritis. Br J Rheumatology 1997; 36(12): 1189-95.