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RELATIONSHIP OF SUBCLINICAL RENAL DYSFUNCTION AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN RHEUMATOID ARTHRITIS

ROMATAİD ARTRİTTE SUBKLİNİK RENAL DİSFONKSİYON İLE RENİN-ANJİOTENSİN-ALDOSTERON SİSTEMİ ARASINDAKİ İLİŞKİ

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SUMMARY

Rheumatoid Arthritis (RA) is a chronic, systemic disease with unknown etiology. Although it characteristically presents with articular findings, it may also show extraarticular involvement. Extraarticular manifestations are various, and one of them is renal involvement.

The purpose of this study was to investigate the subclinical renal dysfunction in RA and its relationship with renin-angiotensin-aldosteron system. In addition it was to determine whether there is a connection between duration, severity of RA and the degree of renal disorder.

We studied 20 patients with RA (17 female, 3 male) diagnosed according to American Rheumatism Association (ARA) 1987 revised criteria. Eighteen patients (3 male, 15 female) that admitted to the out-patient clinic with the clinical and radiological evidence of large joint osteoarthritis (OA) were chosen as the control group.

We found statistically significant increase in the levels of blood urea nitrogen (BUN) and proteinuria, significant decrease in the levels of creatinine clearence and plasma renin activity (PRA) in the RA group compared to the control group. This study suggests that routine renal function tests are important for demonstrating renal involvement in the patients with RA, but renal biopsy should be performed to establish involvement of the kidneys in RA.

Key words : Rheumatoid Artritis, subclinical renal dysfunction, renin-angiotensin-aldosterone system

ÖZET

Romatoid Artrit etiyolojisi bilinmeyen, kronik ve sistemik bir hastalıktır. Karakterisitik olarak bir eklem hastalığı olmasına rağmen, ekstraartiküler tutulum da gösterebilir. Ekstraartiküler bulgular çok çeşitlidir ve onlardan biri de böbrek tutulumudur.

Bu çalışmanın amacı RA'teki subklinik renal disfonksiyonu ve bunun Renin-Angiotensin-Aldosteron sistemi ile ilişkisini araştırmaktır. Aynı zamanda hastalığın şiddeti ve süresi ile renal bozukluğun derecesi arasında bir ilişki olup olmadığını saptamaktır. Bu amaçla 1987 ARA kriterlerine gore RA tanısı almış 20 hasta (17 kadın, 3 erkek) çalışmaya alındı. Polikliniğimize başvuran klinik ve radyolojik olarak büyük eklem osteoartriti tanısı almış 18 hasta (15 female, 3 male) kontrol grubu olarak seçildi.

Çalışmamızda RA'li hastalarda kontrol grubuna gore BUN ve proteinüri değerlerinde istatistiksel olarak anlamlı bir artış, kreatinin klirens ve PRA'nde ise anlamlı azalma bulduk. Bu çalışma göstermiştir ki, rutin böbrek fonksiyon testlerinin renal tutulumdan şüphelenilen RA hastalarında yapılması önemlidir, an-

INTRODUCTION

RA is a chronic and systemic disease with unknown etiology. Although characteristically an inflammatory arthritis of peripheral joints, it may also show extraarticular findings and one of them is renal involvement (1). Kidneys are rarely involved directly but often indirectly in RA . Renal damage is frequently detected in autopsy studies, but is less apparent in living RA patients (2).

Many causes of renal disorders are distinguished in RA. Possible causes are amyloidosis, vasculitis and drug therapies. The changes of renal functions in RA are usually unnoticed or subclinical. A correlation between the severity, the duration of

the disease, positivity of rheumatoid factor (RF)and renal dysfunction has been demonstrated (3).

We studied 20 patients with RA in order to investigate the relationship of renin-angiotensin-aldosteron system and subclinical renal dysfunction and to demonstrate if there is a relation between the severity, duration of disease and the degree of renal disorder.

MATERIAL AND METHOD

This study included 20 patients with RA having proteinuria and hematuria, admitted to the Ankara Hospital Physical Medicine and Rehabilitation clinic through September 1993 to June 1995. Eighteen patients with osteoarthritis without history of hypertension were included to the study as the control group.

Among 20 patients diagnosed as RA according to the American Rheumatism Association (ARA) 1987 revised criteria (4), 17 were female and 3 were male. Mean of the age of the patients was 50.6±17.6 years. The duration of the disease averaged 12.3±9.4 years.

A detailed interrogation of systems and physical examination were performed in all patients. Laboratory examinations included urine analyses, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), Rose-Waller test (RW), BUN, creatinine, Na, K, total protein, albumin, protein electrophoresis, PRA, serum aldosteron levels, 24-hours urine creatinine and protein. Abdominal ultrasonography (USG) was performed to all of the patients. PRA was measured by Clinical Assay X-Coat PRA I 125 RIA in the Nuclear Medicine Laboratory of Faculty of Medicine Gazi University. All the other laboratory examinations were performed in the biochemistry and microbiology laboratories of the Ankara Hospital.

Eighteen patients (3 male, 15 female) admitted to out-patient clinic, clinically and radiologically diagnosed as large joint osteoarthritis were chosen as the control group. Mean age was 57±6.2 years. The same examinations were also performed in all cases of the control group.

RA patients were functionally and radiologically staged according to Steinbrocker's classification (5) . Functionally, 3 of the 20 patients presented in stage I, 5 of them in stage II, 7 of them stage III, and 5 of them stage IV. [I2]Radiologically , one had stage I, 7 had stage II, 8 had stage III, and 4 had stage IV manifestations of the disease.

RA patients were receiving antimalarial agents, sulphasalasine, cyclosporine, corticosteroids or NSAIDs alone or in combination therapy. None of them had previously received gold salts and D-penicillamine.

In this group, one patient had Sjögren's syndrome, another one had Parkinson's disease.

In the control group, all of the patients were receiving NSAID's.

Table I summarizes the clinical characteristics of the RA patients.

In statistical analysis, the Mann-Whitney-U test and the Pearson correlation analysis were used.

Table I: Characteristics of patients with RA

RA (n=20)			
Age (year)		50.6±17.6	
Sex (F/M)		17/3	
Disease duration (year)		12.3±9.4	
Functional stage I			3 (15 %)
stage II		5 (25 %)	
stage III		7 (35 %)	
stage IV		5 (25 %)	
Radiological stage I			1 (5 %)
stage II		7 (35 %)	
stage III		8 (40 %)	
stage IV		4 (20 %)	
RF (+)/(-)		16/4 (80/20 %)	
CRP (+)/(-)		15/5 (75/25 %)	
Drug therapy			
NSAI	3 (15 %)		
NSAI+DMARD' s*	16 (80 %)		
NSAI+DMARD's +Steroid		1 (5 %)	

***DMARD's:** Disease Modifying Antirheumatic Drugs

Table II: The mean laboratory values of RA and control group.

	RA (n=20)	Control (n=18)	p
Age (year)	50.6±17.6	57.7±6.2	>0.05
ESR (mm/h)	65.5±33.5	15.6±9.9	<0.05
Proteinuria (mg/24 h)	76.2±22.5	---	
Leucosyturia	Slight	---	
Hematuria	Slight	---	
BUN (mg/dl)	28.8±17.4	16.2±4.3	<0.05
Serum creatinine (µmol/l)	92±21	94±15	>0.05
UrineCreatinine (mmol/24 h)	12.97±5.13	13.47±4.31	>0.05
CrCl (ml/min)	109.6±135	110.8±32.2	<0.05
PRA (ng/ml/h)	0.39±0.44	0.81±0.57	<0.05
Aldosterone (pg/ml)	92.3±87.5	106±52.3	>0.05

RESULTS

The mean clinical and laboratory findings within groups given in Table II.

There were no statistically significant differences between the groups on age and sex.

ESR was 65.5±33.5 (15-115) mm/h in RA group, but in the control group it was 15.6(9.8 (4-40). CRPwas 30±30.3 (0-118) mg/dl in the RA group, and 1.7±3.5 (0-10) mg/dl in the control group. The levels of ESR and CRP in RA were statistically higher than those in OA ($p<0.05$).

In the urine analysis, 9 patients with RA had pyuria and 3 had hematuria. All of the patients with RA had proteinuria, with a mean value of 76.6±22.5 mg/24-hours . None of the patients in the control group had protein in the 24-hours urine sample. In RA patients the mean serum creatinine concentration was measured as 92±21 (70-150) µmol/l and the mean urinary creatinine excretion was 12.97±5.13 (5-24) mmol/24 hours. In the control patients the mean serum creatinine concentration was 94±14 (80-120) µmol/l and the mean urinary creatinine excretion was 13.47±4.31 (60-120) mmol/24 hours. There were no difference between two groups in respect to these results ($p>0.05$).

The creatinine clearance was 109.6±135 (31-666) ml/min in RA and 110.8±32.2 (46-157) ml/min in the OA group. It is significantly lower in RA group than in OA group(p(0.05).

Mean BUN level was 28.8±17.4 (7-74) mg/dl in the RA group and 16.1±4.36 (5-21) mg/dl in the OA group ($p<0.05$).

PRA was 0.39(0.40 (0.13-2) ng/ml/hr in the RA and 0.81±0.50 (0.2-2.2) ng/ml/hr in the control group. Serum aldosterone level was 92.3±87.5 (48-324) pg/ml in the RA group and 106(52.3 (25-182) pg/ml in the control group. When compared with the control group, PRA was significantly lower in the RA patients ($p<0.05$), while there was no statistically significant difference concerning serum aldosterone levels ($p<0.05$).

Serum protein was detected as 7.7±0.7 (6.4-9) g/dl in the patients with RA and 7.3±0.7 (5.9-8.2) g/dl in the OA group ($p<0.05$). Protein electrophoresis revealed similar results in both groups: albumin was 41±7 (26.3-53.1) g/dl and 41.7±3.2 (36.9-50.2) g/dl; (1-globulin was 3.76±0.6 (2.4-0.7) g/dl and 3.7±0.5 (2.4-4.5) g/dl; α2-globulin was 14.3±1.7 (11.4-17) g/dl and 15.5±2.5 (12.3-20.2) g/dl; (-globulin was 15.4±2.9 (8.6-19.7) g/dl and 17.2±2.5 (13.5-22.1) g/dl; gamma-globulin was 24±6 (15.5-38) g/dl and 21.5±2.5 (17.4-27.4) g/dl in the RA and OA groups, respectively ($p<0.05$).

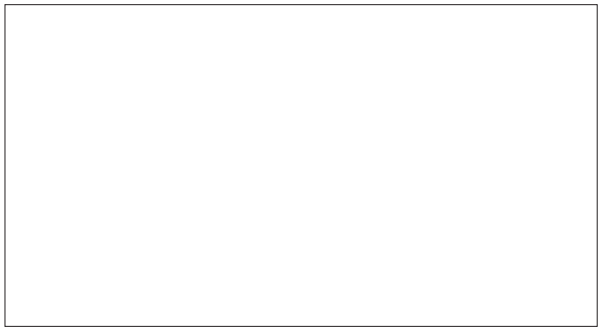

Figure 1: BUN and Creatinine Clearence (CrCl) values of RA and control group.

Figure 2: Serum creatinine and PRA values of RA and control group.

The results of BUN, creatinine clearance, creatinine and PRA of RA and OA patients are given in Figures 1 and 2.

ESR levels was found to be correlated with the levels of BUN (r= 0.39, p<(0.05); PRA (r= -0.40, p<0.05) and aldosterone (r= -0.29, p(0.05). There was no correlation between duration of the disease and ESR. While no correlation between systolic blood pressure and PRA has been demonstrated, a correlation between diastolic blood pressure and PRA has been detected (r= 0,30, p<0.05).

In a patient with proteinuria of 95 mg/dl in spot urine sample and protein of 1 g in 24-hours urine, bilateral pyelitis and crystaloids have been demonstrated in the renal USG. This patient has underwent renal biopsy. Examination of the specimen revealed a normal structure of renal medulla.

DISCUSSION

Although major signs and symptoms of the RA are related to the joints, it may also involve other organs and systems. Manifestations of these involvement may vary from mild dysfunction to severe conditions that may end with death.

In renal involvement seen in RA, damage of the functions of kidneys is usually slight and clinically of no importance. However, 20% of the deaths are due to renal damage in RA . While in autopsy studies renal involvement is often and appearant, subclinical picture exist in most of the living RA patients (3,15). Is there renal involvement in every patient with RA and what are the clinical and laboratory findings that will help us?

There are few studies in the medical literature about renal involvement in RA and the results of them are controversial.

Boers et al. studied 35 chronic seropositive RA patients in order to investigate whether vasculitis and hypergamaglobulinemia were risk factors in renal dysfunction. Eight of 35 patients had decreased GFR, 11 had microproteinüria, 10 had abnormal urine concentration capacity and 15 had increased enzymes of urinary tubules. They demonstrated a negative correlation between GFR, creatinine clearence and duration of the disease, age of the patients. As a result , they concluded that subclinical renal dysfunction was frequently seen in chronic seropositive RA patients and vasculitis and hypergamaglobulinemia were not considered as risk factors in RA (6).

In another study by Boers et al., PRA was measured in 34 patients with RA, 7 of whom had rheumatic vasculitis in order to evaluate if plasma renin and its inactive precursor prorenin could be a marker of vasculitis in RA. In RA patients with vasculitis, they found that the levels of renin and prorenin were higher than those without vasculitis. Creatinine clearence has been same in both groups. Plasma aldosterone concentration has been elevated slightly in 2 patients without vasculitis and elevated considerably in a patient with vasculitis. However, they could not establish a correlation between renin, prorenin levels and age, sex, duration of the disease, antirheumatic and immunosuppressive therapy. In the light of these findings, they concluded that RAA system was activated, and this could be an early manifestation of cardiac and renal vasculitis (7).

Many investigators studied frequency and severity of renal dysfunction in RA patients by using sensitive tests of tubular and glomerular function and they found decreased creatinine clearence in 26 %, dysmorphic hematuria in 40 % and increased microalbuminuria in the 5 % of the patients with RA. Investigators have demonstrated a positive correlation between the duration of the disease and these findings. All of the patients were receiving NSAID's, 4 of them were receiving gold salts, 2 of them were receiving D-penicillamine and one of them were receiving sulphasalasine. They concluded that subclinical renal dysfunction are frequently seen in patients with RA and it is probably associated with the long-term drug treatment (8,13,14).

Serum creatinine concentration varies with muscle mass, since it is synthesized in the muscles and excreted through the kidneys. In a study about this subject by Nived et al., serum creatinine levels were measured in rheumatic patients and healthy controls. Most of the patients in this study were receiving one or more drugs as well as corticosteroids. But, there were no demonstrable relation between these drug therapies and serum creatinine concentration and GFR. It is decided that these results are related to severe or moderate muscular atrophy found in most of the patients (9).

In the RA patients, muscle mass is decreased because of inactivity and inflammation. In a study seeking reliability of creatinine clearance in RA patients, Boers et al. demonstrated that creatinine level was not a reliable index in the evaluation of renal function in inflammatory disease (10).

RAA system is activated depending on vasculitis in patients with RA. In recent studies, it has been found that PRA increased in RA, but showed no correlation with CRP (11). In another study, RAA system was investigated in patients with RA. Decreased renin concentration and increased plasma aldosterone and angiotensin II concentration in patients with arteriel hypertension have been determined (12). As a result, immunopatological reactions were thought to be responsible for changes in RAA system in hypertensive RA patients.

In our study, we found significantly high levels of BUN and increased percentage of proteinuria, and significantly lower values of PRA and creatinine clearance in RA patients when compared to the control group. We could not demonstrate a statistically significant difference between two groups when concerned serum creatinine, urine creatine and aldosterone concentrations. Our results were contradictory to the studies that established these parameters as the early manifestation of renal involvement in RA.

In our study, the levels of PRA and aldosterone were not related to disease activity.

S ignificantly low levels of PRA according to the controls may be due to;

■ penetration of renin into the synovial fluid (8),

■ suppression of renin depending on diastolic hypertension (12).

In conclusion, we thought that routine renal function tests is of importance in RA patients in whom renal involvement is considered. Yet it should be kept in mind that renal biopsy is necessary in showing whether there is definite involvement.

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