

Prevalence of biochemical and immunological abnormalities in rheumatoid arthritis

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Summary

The prevalence of biochemical and immunological abnormalities was studied in a group of 256 patients with rheumatoid arthritis (104 coloureds, 100 whites and 52 blacks). The most common biochemical abnormalities detected were a reduction in the serum creatinine value (43,4%), raised globulins (39,7%), raised serum alkaline phosphatase level (42,3%), reduction in serum albumin value (8,1%), a mild rise in serum creatinine value (6,6%), and a raised serum γ -glutamyltranspeptidase (GGT) level (6,5%). The prevalence of a rise in the GGT was less frequent than reported in other published studies. The immunological abnormalities noted were a positive rheumatoid factor (78,9%), positive anti-nuclear factor (36%), raised serum IgG (43,3%) and IgA (10,5%) values, positive smooth-muscle antibody (12,5%) and elevated double-stranded anti-DNA antibody levels (2,3%). Inter-group comparisons showed that the serum IgG and IgA and total globulins were significantly higher in blacks and coloureds than whites; these findings may be related to a higher prevalence of malnutrition and infection in childhood in these communities. There were no significant inter-group differences that could be attributed to rheumatoid arthritis.

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Rheumatoid arthritis (RA) is a systemic disease characterised by the occurrence of articular and extra-articular manifestations. Biochemical and immunological abnormalities are also frequently noted. The presence of rheumatoid factor (RF) is a feature of the disease; it is detected in about 75% of patients with RA.¹ Other immunological abnormalities detected are a positive antinuclear factor (ANF),² raised serum immunoglobulin values,³⁻⁵ raised circulating immune complexes⁶ and, less frequently, hypocomplementaemia.⁷ Biochemical abnormalities may be related to the disease *per se*, while others may be related to the complications of the disease or therapy. Raised alkaline phosphatase and γ -glutamyltranspeptidase (GGT) levels have frequently been detected in RA and have been correlated with the activity of the disease.⁸⁻¹⁰ A reduction in the serum creatinine value¹¹ and abnormalities of calcium and cholesterol have also been reported.^{12,13}

Although individual biochemical and immunological abnormalities in RA have been reported in different studies, this survey was undertaken to determine the prevalence of several of the biochemical and immunological abnormalities in a large group of patients from three different communities and to determine whether there were any inter-group differences.

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Patients and methods

The prevalence of laboratory abnormalities in RA was studied as a part of a more extensive survey on the spectrum of RA. Some aspects of the survey have already been published.¹⁴⁻¹⁸ The selection of patients and demographic data has been reported previously,¹⁴⁻¹⁵ and are included here, since they assist with the interpretation of results. All patients with classic or definite RA¹⁹ who were seen in the Rheumatic Diseases Unit at Groote Schuur and Princess Alice Orthopaedic Hospitals in Cape Town over a 16-month period preceding the survey were considered eligible for inclusion in the study. There were a total of 330 coloureds, 203 whites and 55 blacks, who had been seen on one or more occasions during this period. Random number tables were used to select the 104 coloureds and 100 whites who were entered into the study. A smaller number of blacks are seen in the unit and the 52 patients who agreed to take part were included in the study. Although blacks constitute the majority population in South Africa, the number of blacks resident in the Cape Peninsula is less than elsewhere in the RSA. The number of patients with RA from the different communities who were seen is roughly proportional to their representation in the local community.

All patients were interviewed and their ages, duration of RA and American Rheumatism Association (ARA) functional classification²⁰ were recorded. The clinical records of all patients were reviewed. The following tests were performed: blood urea estimation, measurement of electrolyte, creatinine, calcium, phosphorus, albumin, globulin, GGT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase values (Technicon SMAC 12 autoanalyser); the levels of immunoglobulins G, A and M (Behring laser nephelometer); presence and titre (1/80 or higher was considered seropositive) of RF (latex test — slide agglutination technique (Ortho Diagnostics); ANF, smooth muscle antibody and antimicrobial antibody (indirect immunofluorescent technique); and level of double stranded anti-DNA antibody (DS-DNA) (Millipore filtration technique).²¹

Statistical analysis. For categorical data, the three groups were compared using the Pearson chi-square test, and Fisher's exact test for 2×2 tables was used when pairwise comparisons were made. For continuous data, the three groups were compared using the one-way analysis of variance followed by the *t*-test for pairwise comparisons. The test level of significance for the various pairwise comparisons was adapted according to Bonferroni²² for the multiple comparisons done.

Results

The female:male ratio was 2,8:1 and there were no significant differences between the three communities. The mean age of the patients was $52,8 \pm 12,8$ years (coloureds $51,1 \pm 12,0$, whites $58,9 \pm 12,2$ and blacks $44,6 \pm 9,7$ years). The whites were significantly older than the coloureds and blacks ($P < 0,0001$) and the coloureds were significantly older than the blacks ($P = 0,0011$). The mean duration of RA was $12,3 \pm 9,3$ years (whites $14,4 \pm 9,7$, coloureds $12,4 \pm 9,3$ and blacks $8,2 \pm 7,3$ years). The duration of RA was significantly lower in blacks in comparison with coloureds ($P = 0,0026$) and whites

($P = 0,0001$). The ARA functional classification of the patients was as follows: class 1 — 66 patients (25,8%); class 2 — 134 patients (52,3%); class 3 — 37 patients (14,5%) and class 4 — 19 patients (7,4%). There were no significant differences in the functional classification between the different population groups.

The mean values for the biochemical tests and serum immunoglobulin values in the three different population groups are shown in Table I. There were no significant differences in the serum albumin, calcium, uric acid, alkaline phosphatase and IgM levels. There was a relationship between age and the serum urea and creatinine values. The mean blood urea measurements in the three groups differed significantly from each other. The serum creatinine values in blacks were significantly lower than in coloureds ($P = 0,0036$) and whites ($P < 0,0001$). The total serum globulin and IgG values were significantly higher in coloureds and blacks than in the whites ($P < 0,0001$). The serum IgM levels were higher in coloureds ($P = 0,0017$) and blacks ($P = 0,0106$) when compared with whites. The mean cholesterol values were lower in blacks than in coloureds ($P = 0,0001$) and whites ($P < 0,0001$).

The mean values for the biochemical tests and the immunoglobulin values in the total study population and the prevalence of abnormalities are shown in Table II. The serum alkaline phosphatase level was elevated in 107 patients (42,3%) and the majority of these patients had a less than two-fold increase. The serum GGT value was elevated in only 14 of the 216 patients (6,5%) in whom it was measured. Twelve patients with an elevated serum GGT value also had elevated serum alkaline phosphatase values. The serum LDH level was elevated in 2 patients (0,8%), AST in 2 patients (0,8%) and ALT in 3 patients (1,2%). The elevation of the serum LDH, AST and ALT levels was less than two-fold in all patients. The total serum bilirubin value was marginally elevated in 1 patient (19 $\mu\text{mol/l}$; normal 0-17 $\mu\text{mol/l}$).

There were 72 patients (28,1%) who had an elevated blood urea value ($> 6,7 \text{ mmol/l}$) but the degree of elevation was mild in the majority, since the mean value was $5,9 \pm 2,5 \text{ mmol/l}$ (Table II). There were 17 patients (6,6%) who had an elevated blood urea value of $> 10 \text{ mmol/l}$. The serum creatinine value was elevated in 17 patients (6,6%) and in these patients the mean level was $133,4 \mu\text{mol/l}$ and the mean blood

TABLE I. COMPARATIVE BIOCHEMICAL FINDINGS IN THE THREE POPULATION GROUPS (MEAN \pm SD)

Biochemical measurements	Coloureds	Whites	Blacks	Significant differences
Albumin (g/l)	40,0 \pm 4,2	39,9 \pm 4,7	38,4 \pm 3,6	—
Globulin (g/l)	36,6 \pm 8,7	29,9 \pm 7,1	38,5 \pm 7,9	1
IgG (g/l)	19,81 \pm 8,18	14,98 \pm 5,3	22,45 \pm 6,77	1
IgA (g/l)	4,51 \pm 2,46	3,49 \pm 1,95	4,44 \pm 2,13	1
IgM (g/l)	2,28 \pm 1,65	1,93 \pm 1,09	2,33 \pm 1,55	—
Cholesterol (mmol/l)	5,36 \pm 1,15	5,65 \pm 1,27	4,54 \pm 0,97	2
Calcium (mmol/l)	2,40 \pm 0,11	2,38 \pm 0,13	2,36 \pm 0,12	—
Urea (mmol/l)	5,8 \pm 2,5	6,7 \pm 2,5	4,5 \pm 1,77	3
Creatinine ($\mu\text{mol/l}$)	80,7 \pm 19,5	87,3 \pm 22,6	70,7 \pm 15,8	2
Uric acid (mmol/l)	0,36 \pm 0,10	0,34 \pm 0,09	0,32 \pm 0,08	—
Alkaline phosphatase (U/l)	111,1 \pm 34,2	113,5 \pm 38,4	114,6 \pm 36,1	—

Significant differences: 1 = all three groups differed significantly from each other; 2 = coloureds and whites were significantly different from blacks; 3 = coloureds and blacks were significantly different from whites.

TABLE II. PREVALENCE OF BIOCHEMICAL ABNORMALITIES

	Normal range	Mean values	% abnormal	
			Present study	Cockel <i>et al.</i> ²³
Urea (mmol/l)	1,7 — 6,7	5,9 \pm 2,5	28,1 high	16 high
Creatinine ($\mu\text{mol/l}$)	75 — 115	81,3 \pm 20,9	6,6 high 43,4 low	7 high
Uric acid (mmol/l)	0,12 — 0,45	0,34 \pm 0,09	12,1 high	8 high
Albumin (g/l)	35 — 50	39,6 \pm 4,3	8,1 low	25 low
Globulin (g/l)	25 — 35	34,4 \pm 8,7	39,7 high 0,4 low	44 high
Cholesterol (mmol/l)	3,1 — 7,1	5,30 \pm 1,23	7,8 high	4 high
Calcium (mmol/l)	2,10 — 2,60	2,39 \pm 0,12	2,8 high	20 low 1 high
Alkaline phosphatase (μl)	30 — 115	112,8 \pm 36,2	42,3 high	26 high
LDH (U/l)	100 — 350	201,1 \pm 46,6	0,8 high	-
AST (U/l)	0 — 40	15,8 \pm 6,3	0,8 high	-
ALT (U/l)	0 — 53	17,3 \pm 11,1	1,2 high	-
GGT (U/l)	0 — 50	15,9 \pm 23,1	6,5 high	-

urea value was 10,7 mmol/l. A reduction in serum creatinine level (less than 75 $\mu\text{mol/l}$) was much more common and was noted in 111 patients (43,4%).

The serum uric acid value was elevated ($> 0,45$ mmol/l) in 31 patients with 14 having a mild elevation (0,46 - 0,50 mmol/l); the remaining 17 had levels $> 0,50$ mmol/l. Eighteen of these patients were on diuretic therapy or had an elevated serum creatinine level. One patient had a mild elevation of the blood urea value (7,4 mmol/l) with a normal serum creatinine value, and the remaining 12 patients (4,7%) had elevated uric acid levels without any obvious secondary cause. A raised serum calcium level ($> 2,6$ mmol/l) was detected in 7 patients but none had a reduction in serum calcium values after correction for hypo-albuminaemia.

A rise in the serum immunoglobulin values was frequently noted, with 106 patients (43,3%) having a raised IgG level, 63 patients (25,9%) a raised IgA level and 23 patients (10,5%) a raised IgM level. Only 1 patient had a reduction in serum immunoglobulin value, with a reduction of both IgG and IgA levels. A positive latex test for RF was noted in 61% of patients at the time of assessment and a total of 78,9% had a positive RF at some time during the course of their disease. Ninety-one patients (36,0%) had a positive ANF in a titre of 1/10 or higher. The pattern of nuclear fluorescence was speckled in 75 patients (29,6%) and homogeneous in 13 (5,2%); this information was not available in 3 patients. There was a mild elevation of the DS-DNA in 6 patients (mean value 28 ng/ml bound DNA/ml of serum; range 22-40 ng/ml). Two of these patients had a positive RF and ANF, 1 patient had a positive ANF alone and 1 patient had a positive RF alone. Two patients had a negative RF and ANF.

The smooth-muscle antibody was positive in a titre of 1/10 in 14 patients (5,5%) and 18 patients (7,0%) had a titre of 1/20 - 1/80. One patient with a positive smooth-muscle antibody in a titre of 1/10 had an elevated serum LDH value of 513 U/l but the serum transaminase level was normal. The antimitochondrial antibody was positive in only 1 patient, in a titre of 1/10. The patient with a positive antimitochondrial antibody and all the other patients with a positive smooth-muscle antibody had normal serum LDH and transaminase values.

There were no significant differences between the races for the prevalence of a positive RF, ANF, smooth-muscle antibody or raised DS-DNA levels.

Discussion

The prevalence of abnormalities of serum biochemical values was reported by Cockel *et al.*²³ in a group of 100 patients with RA and their findings are compared with our results in Table II. A reduction in the serum albumin value and a rise in the serum globulin value have been reported previously²³⁻²⁵ and were noted in 25% and 44%, respectively, by Cockel *et al.*²³ and 9,1% and 39,7%, respectively, of our patients.

A rise in the serum alkaline phosphatase level has been reported in 18 - 46% of patients with RA^{8,23,26-28} and was detected in 42% of our patients. A rise in the serum alkaline phosphatase level has been associated with a raised serum 5-nucleotidase, elevation of serum GGT values and disease activity.^{25,26} Lowe *et al.*⁹ found an elevated serum GGT value in 73% of their 62 patients but Spooner *et al.*⁸ found an elevated serum GGT value in only 23,5% of their 98 patients and only 12% had elevated serum GGT and alkaline phosphatase levels. We found that only 14 of our patients (6,5%) had elevated serum GGT levels and 12 of these patients also had elevated serum alkaline phosphatase values. In a recent study, Thompson and Kirwan²⁹ noted that serum AST, ALT and GGT levels were generally normal in RA but serum

alkaline phosphatase and 5-nucleotidase levels were elevated in 25% and 31%, respectively. They suggested that the elevated serum alkaline phosphatase value was due to diffusion from the joints as the synovial fluid to serum ratio was 6,9 and the alkaline phosphatase probably came from osteoblasts involved in the repair of tendons.

Hyperuricaemia may develop in RA as a result of salicylate therapy, rapid tissue breakdown and silent pyelonephritis.^{23,30} Cockel *et al.*²³ found an elevated uric acid level in 8 of their 100 patients and this was attributed to renal impairment in 7. We found that 12,1% of our patients had a raised serum uric acid level but only 4,7% did not have any secondary cause for the hyperuricaemia; the raised serum uric acid value in these patients is similar to the prevalence of hyperuricaemia in the normal population.³¹

A reduction in serum creatinine value has been reported in patients with rheumatic diseases.¹¹ We have reported a reduction in the serum creatinine level (< 75 $\mu\text{mol/l}$) in 43,4% of our patients.¹⁸ Thus our observation supports the suggestion by Nived *et al.*¹¹ that lower normal values may need to be considered when assessing the significance of serum creatinine values in RA. A rise in the blood urea level of more than 10 mmol/l in 6,6% of our patients is similar to the 5,4% of 167 patients reported by Richards *et al.*³² Sorensen³³ found a reduction in creatinine clearance in 32% of 203 patients with RA in comparison with a prevalence of 13,8% in a control group of 447 patients. The impaired renal function in these patients was dependent on the duration and severity of the disease. The factors which contribute to impaired renal function in RA are nephrotoxicity related to non-steroidal anti-inflammatory drugs and immunomodulatory drugs, such as gold and penicillamine, the presence of co-existent hypertension and cardiac diseases and the older age of the patients. A variety of renal effects have been reported with non-steroidal anti-inflammatory drugs and they now constitute an important and potentially reversible cause of impaired renal function in RA.³⁴

Abnormalities of serum immunoglobulin values have been noted frequently in previous studies.³⁻⁵ Tilve *et al.*⁴ studied 50 patients with RA and found elevated IgM levels in 14%, elevated IgG and IgM levels in 22%, a reduction in IgG level in 10% and reduction in both IgG and IgM levels in 6%. In another study of 80 patients, Pruzanski *et al.*⁵ found an increased IgG level in 15% and IgM in 6%, and a reduction of the IgG level in 1% and IgA in 19%. In the present study only 1 patient had a reduction of both IgG and IgA levels, while raised IgG (43,3%), IgA (25,9%) and IgM (10,5%) levels were common.

The prevalence of a positive RF in 78,9% of our patients is similar to the prevalence of 75% reported by Davis.¹ An increased prevalence of a positive RF has been reported in hospitalised black patients without any joint disease^{35,36} but we did not detect any differences between the three groups studied.

Pollak² detected antinuclear antibodies in 24% of his 72 patients and a similar prevalence of 24% in a review of 638 patients with RA. Webb *et al.*²⁷ found a positive ANF in 34,4% of their 216 patients and a similar prevalence of 36% was noted in the present study. Antibodies to DS-DNA are characteristically found in patients with systemic lupus erythematosus but were also detected in 4,8 - 16% of RA patients.³⁷⁻³⁹ Rochmis *et al.*³⁹ found that all 3 of their 62 RA patients with DS-DNA antibodies (4,8%) had negative antinuclear antibodies and two had negative RF tests. We found a mild elevation of DS-DNA antibodies in 6 patients (2,4%).

Antimitochondrial antibody was detected in 10% of 71 patients by Doniach *et al.*⁴⁰ while Whaley *et al.*⁴¹ estimated a prevalence of 0,94% in 997 patients with RA alone and 1,5% in 71 patients with RA and Sjögren's syndrome. A positive

smooth-muscle antibody was present in 16% of 32 patients studied by Doniach *et al.*⁴⁰ We found only 1 patient (0,4%) with a positive antimitochondrial antibody and 32 patients (12,5%) had a positive smooth-muscle antibody.

In the inter-group comparison, the significantly higher mean blood urea and serum creatinine values in whites in comparison with blacks were probably related to the higher mean age of the whites in the study, since there was a relationship between age and the level of the blood urea and serum creatinine. A high serum cholesterol level is recognised as one of the risk factors for ischaemic heart disease and the significantly lower cholesterol values in blacks is probably a contributory factor to the lower prevalence of ischaemic heart disease in this population group. The serum globulin and IgG values were significantly higher in blacks and coloureds and this may be due to the higher prevalence of malnutrition and infection in childhood and also the increased frequency of liver disease in these communities.⁴²

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