PAPERS AND ORIGINALS

Renal disease in rheumatoid arthritis

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British Medical Journal, 1976, 1, 611-612

Summary

N-Acetyl- β -D-glucosaminidase (NAG) is a sensitive indicator of renal damage. When the urinary NAG levels of 60 patients with rheumatoid arthritis (RA) were measured a highly significant difference was detected between the mean urinary NAG excretion of the patients with RA (341 ± 294.92 nmol h⁻¹ mg creatinine⁻¹) and that of 60 matched controls (67.53 ± 16.93 nmol h⁻¹ mg creatinine⁻¹). In 10 patients studied no correlation could be shown between the urinary NAG levels and levels in either serum or synovial fluid. A significant positive correlation was noted between urinary NAG excretion and disease activity as estimated by the Lansbury activity index, the Ritchie articular index, and the haemaglobin level. An abnormally raised urinary NAG excretion was detected in eight out of 20 previously untreated patients with RA, which suggested that the rheumatoid process may affect renal function.

Introduction

In patients with rheumatoid arthritis (RA) there is a high incidence of impaired renal function, with evidence of reduced glomerular filtration¹⁻⁴ and tubular function.⁵ Structural changes have also been found at necropsy in the kidneys of 72% of sufferers from RA compared with 25% of a control group.⁶ Nevertheless, it is difficult to differentiate between the disease itself and drug treatment as the cause of the renal damage.

Excretion of β -glycosidase enzymes is increased in several renal diseases,⁷ and measurement of *N*-acetyl- β -D-glucosaminidase (NAG) is a simple and sensitive test of renal damage that is currently used as an early warning of renal graft rejection.⁸ A

preliminary study suggested that excretion rates of this enzyme were increased in RA and that its measurement might prove a useful test for renal damage and nephrotoxicity in this disease.⁹ We report here the results of an expanded study of NAG excretion in RA, in which enzyme levels were correlated with disease duration and activity.

Methods

All subjects were aged 25 to 75 years and fulfilled the American Rheumatism Association (ARA) criteria for classical or definite RA.^{10 11} All patients with known past or present renal disease, hypertension, proteinuria, or clinical evidence of Sjögren's syndrome were excluded. Blood and urine samples were collected from the patients during routine assessment, and synovial fluid samples were collected when joint aspiration was justified on clinical grounds. Blood and urine were also collected from normal volunteers for comparison.

Disease assessment—On the day samples were collected the disease activity was assessed by measuring haemoglobin, erythrocyte sedimentation rate (ESR) (Westergren), differential agglutination titre (DAT), grip strength, articular index (Ritchie¹²), and early morning stiffness. The activity index was calculated by the method of Lansbury¹³⁻¹⁵ using the Ritchie articular index in place of the originally described joint score, the Ritchie index being given the equivalent percentage weighting in the overall score. The age, sex, past and present treatment, and length of disease were recorded in all cases.

Measurement of NAG—Blood and synovial fluid samples were collected into plain sterile containers, centrifuged, and the supernatant stored at 4°C before measurement. Urine samples were stored at 4°C in sterile containers without preservative. NAG was estimated by an automated fluorimetric method.¹⁶ The urinary creatinine was measured by Technicon AutoAnalyzer and the results on random urine samples expressed as nmol h⁻¹ mg urinary creatinine.¹⁷ Isoenzyme patterns were detected by a chromatographic technique.¹⁸

Student's *t* test for independent variables was used to analyse the results.

Results

Urinary NAG activity—Urinary excretion of NAG was measured in 60 patients with RA and 60 controls matched for age and sex. Patients with RA had much higher enzyme excretions than controls ($P < 0.001$; table I).

Serum and synovial fluid NAG activity—Serum NAG activity was estimated in 25 patients with RA and 25 normal volunteers whose average age was slightly below that of the patients with RA. A small increase in serum NAG activity in the RA group was found (table I). In 10 patients with RA enzyme activity was measured in urine,

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TABLE I—Urinary NAG excretion (nmol h⁻¹ mg creatinine⁻¹) and serum NAG concentrations (nmol/l) in controls and patients with RA

	Urinary NAG		Serum NAG	
	Patients with RA	Controls	Patients with RA	Controls
No of patients (women)	60 (39)	60 (39)	25 (18)	25 (13)
Mean age (years)	52.4 ± 12.16	50.45 ± 13.76	46.12	35.6
Mean NAG (nmol)	341.42 ± 294.92	67.53 ± 16.93	288.38 ± 61.68	248.72 ± 60.67
Difference	t = 6.94; P < 0.001		t = 2.42; P < 0.05	

serum, and synovial fluid samples that had been collected on the same day. These samples were also used for estimating the isoenzyme patterns in the three fluids. The NAG isoenzyme pattern in the urine was similar to that in renal tissue—namely, As + B (using the notation of Ellis *et al*¹⁸)—and the isoenzyme patterns in serum and synovial fluid were similar—A + B. The NAG activity in synovial fluid and urine was higher than that in the serum. There was no correlation between serum, urine, and synovial fluid NAG levels in the different samples: synovial fluid (509.6 ± 288.6 nmol/l) *v* serum (288.0 ± 46.6 nmol/l) *r* = 0.28; synovial fluid *v* urine (669.9 ± 393.9 nmol h⁻¹ mg creatinine⁻¹) *r* = 0.3; serum *v* urine *r* = 0.43.

Correlation of urinary NAG levels with disease activity—In 60 patients with RA the urinary activity of NAG was correlated with various indices of disease activity and with the duration of the disease. There was no correlation with the duration of the disease, but there was a significant correlation with several of the measurements used to assess the activity of the disease (table II).

Urinary NAG excretion in untreated RA—In view of complex past and present drug histories and the high incidence of multiple drug treatment formal correlation of NAG excretion with drug intake was not possible. To estimate whether rheumatoid disease alone influenced the urinary activity of NAG urinary NAG measurements were made in 20 patients (10 men and 10 women with a mean age of 50.55 ± 14.32 years) who had had no previous drug treatment for their disease and were on no treatment at the time of assessment. The mean duration of disease in these patients was 2.36 ± 2.95 years and 16 had a DAT greater than 1/4. NAG activity was above 100 nmol h⁻¹ mg creatinine⁻¹ in eight of these 20 patients (compared with one out of 60 controls) and above 200 nmol h⁻¹ mg creatinine⁻¹ in four. The resulting mean activity for the group 133.8 ± 108.43 nmol h⁻¹ mg creatinine⁻¹ was therefore well above that found in the control group.

Discussion

The urinary activity of the enzyme NAG is a sensitive index of renal disease in man⁷ and is currently used as an early warning of renal graft rejection.⁸ A simple automated technique of estimation has been developed¹⁶ and by expressing the results in relation to creatinine excretion errors due to estimating random samples from people with different glomerular function can be overcome.¹⁷ In addition, none of our patients had severely impaired renal function, as measured by 24-hour creatinine clearance. A preliminary study showed that the excretion of NAG was higher in patients with RA than in those with other rheumatological diseases,⁹ and the present study showed that the urinary enzyme activity is much higher in rheumatoid patients than in normal controls. We also found, like others,^{19, 20} that lysosomal enzyme activity is high in rheumatoid synovial fluid. Other workers have also reported an increase in serum NAG activity in RA,^{21, 22} and our results agree with theirs, though the difference from the control group was small and the groups were not perfectly matched for age and sex.

TABLE II—Correlation of urinary NAG concentrations with indices of rheumatoid disease activity

Indices of disease activity:	Age (years)	No with DAT > 1/4	No with nodular disease	Duration of disease (years)	Haemoglobin (g/dl)	ESR (mm in 1 h)	Articular index score	Activity index score
	52.8 ± 12.16	51	12	7.90 ± 6.73	-12.85 ± 1.38	44.98 ± 36.99	17.27 ± 11.26	49.59 ± 29.3
Correlation with NAG				0.07	-0.42; P < 0.01	0.14	0.24; P < 0.05	0.41; P < 0.01

The increase in NAG levels in synovial fluid and serum raised the possibility that the urinary increase was due to filtration of the enzyme. But there are several points against this. Firstly, the enzyme has a molecular weight of 160 000 and should not leak into the urine in the absence of appreciable proteinuria, and all patients with proteinuria were excluded. Secondly, we could not show any correlation between levels of the enzyme in synovial fluid, serum, and urine. Thirdly, the isoenzyme pattern of NAG in urine differs from that in serum and synovial fluid, but it is identical with that found in extracts of renal tissue.¹⁸ This is strong evidence that the urinary enzyme is derived from the kidney.

The positive correlation between urinary NAG activity and indices of disease activity could have two explanations. Either more severe RA tended to affect the kidneys more or patients with more severe disease received more nephrotoxic treatment. Unfortunately, because of the complexity of rheumatoid drug histories, we could not correlate NAG excretion with individual drug treatment, although it was apparent that many patients with the highest levels had had the disease for only a short time and had received little treatment. Other work suggests, however, that salicylates can increase NAG excretion, and that other drugs may have a similar effect, so drugs might have contributed an important part of the overall increase in urinary NAG.^{9, 23, 24}

To try to find out whether rheumatoid disease alone could increase NAG excretion urinary activity was measured in 20 patients who had received no drug treatment for their disease. In eight of these 20 patients levels were abnormally high, which strongly suggested the presence of a renal lesion. Although renal abnormalities are common in RA,⁵ characteristic changes are recognised only with amyloidosis, Sjögren's syndrome, and analgesic nephropathy; no patients with these disorders were included in this study. The evidence therefore favours a renal lesion specific to rheumatoid disease itself.

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