Now and then

The kidney in rheumatic diseases

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Certain rheumatic diseases are associated with unequivocal renal involvement. Examples are the immune complex mediated glomerular nephritis of systemic lupus erythematosus, the renal involvement in other connected tissue disorders such as polyarteritis nodosa, and the renal amyloid that can complicate rheumatoid arthritis or ankylosing spondylitis. Patients with these complications of rheumatic diseases often develop moderate to severe renal impairment making full investigation including renal biopsy ethical as part of the disease management. As a result there are a substantial number of publications on the pathological findings and progression of such complications.

More recently, attention has been directed towards the milder subclinical renal involvement that is increasingly recognised as a feature of rheumatic diseases. Discussion centres on whether this results from the disease, particularly if it has systemic manifestations, or whether it arises from the drug treatment of the disease. Improved methods of monitoring renal function would be welcome but the degree of involvement rarely justifies a renal biopsy. The clinician needs simple tests that can alert him to those patients who may require closer surveillance or be at risk. These practical requirements resemble research needs where examination of the urine, a specimen of which can easily be provided by the patient, might be of value in monitoring the progress of rheumatic disease or the extent of tissue breakdown. For this method to be reliable appropriate correction may be necessary for the effect of the disease or the drug treatment, or both, on the kidney.

An initial study from Leeds showed an unexpectedly high incidence of renal tubular disorders in unselected patients with rheumatic diseases.¹ A more extensive follow up failed to find correlations between the renal tubular defect and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or

disease modifying drugs, frequent urinary tract infections, the presence of hypertension, or the severity of arthritis.² A high degree of proteinuria was associated with increased mortality. Dipstick testing for albumin, though 100% sensitive, has a poor specificity due to a high false positive rate, in some series as high as 48%.³ Microscopic haematuria, unrelated to drug treatment, may occur in rheumatoid arthritis and appears not to have a particularly poor prognosis.⁴ Injectable gold or penicillamine treatment for rheumatoid arthritis can probably be continued in the presence of small amounts of haematuria.⁵

Many patients with rheumatic diseases are elderly and, as a result, require extensive concomitant drug treatment. Interactions between NSAIDs and diuretics are well recognised,^{6,7} particularly when the drugs are used together in the treatment of elderly patients with mild to moderate essential hypertension.⁸ Caution is also required when NSAIDs are prescribed with angiotensin converting enzyme inhibitors. A study of a novel NSAID, tenoxicam, and frusemide given simultaneously for congestive cardiac failure showed a significant drop of prostaglandin E₂ in 12 hour urine specimens but no change in serial creatinine clearance, β_2 microglobulin clearance, or urinary excretion of acetylglucosaminidase.⁹

It has become apparent that creatinine clearance, if carefully monitored (which is not particularly easy in elderly patients), improves when an NSAID is withdrawn and replaced by an analgesic.^{10,11} In a prospective study in which treatment of patients was initially transferred from previous NSAIDs to an analgesic and then to an NSAID for three months the wash out period produced a consistent improvement in creatinine clearance followed by a slight reversible deterioration when the NSAID was introduced (though the degree of impairment, 6–8 ml/min, probably had little clinical relevance and the creatinine clearance actually showed improvement during the initial phases of treatment with the NSAID).¹² It seems that we may have to accept some degree of 'physiological' renal impairment, presumably mediated through inhibition of prosta-

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glandin synthetase in the kidney, whenever NSAIDs are used, though this effect may be more pronounced in patients with severe renal impairment. This realisation has come late in the history of the use of NSAIDs.¹³ By implication the pathological consequences, should any exist, may not be great. Several NSAIDs have now been shown to produce a slight decrease in urinary prostaglandin E among several prostaglandins that have been measured.^{14 15}

The optimum method for determining renal impairment when NSAIDs are used is still open to question. The errors inherent in the use of creatinine clearance in patients with rheumatoid arthritis have been highlighted,¹⁶ and there is a danger that clearance may be overestimated. Both kidney function and muscle mass decline with age so serum creatinine does not rise as much in the elderly as it would in a younger person with the same degree of renal impairment. A fit 70 year old with normal blood biochemistry may have a glomerular filtration rate as low as 30 ml/min. The elderly find it difficult to provide urine samples of reliable volume for the precise estimation of creatinine clearance and an approximation derived from the use of a nomogram for serum creatinine concentrations may be more helpful. The reciprocal of serum creatinine has also been suggested as a good measure of impaired renal function of patients with arthritis.¹⁷

Doubts have been expressed about the value of urinary concentrations of β_2 microglobulin as an index of renal function.¹⁸ β_2 Microglobulin is unstable at pH values less than 5.5 and, rationally, urine from patients could be adjusted by the addition of an alkali. It has been suggested that β -N-acetyl-D-glucosaminidase (NAG), particularly if expressed as an NAG/creatinine ratio, is a more reliable index of renal function than β_2 microglobulin.¹⁹ In some studies the NAG/creatinine ratio has actually improved during treatment with NSAIDs.¹²

The use of urine samples, easily provided by patients, has been suggested for the monitoring of disease progression in arthritis. Pyridinoline provides one example of a protein that probably derives entirely from mature cartilage and which can be measured in the urine.²⁰ Concentrations appear to be independent of factors such as exercise, drug treatment, and renal impairment. Recent work suggests that the pyridinoline/deoxypyridinoline ratio may also reflect bone protein, possibly with implications for the monitoring of osteoporosis.²¹

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