Letters and Replies

Microalbuminuria in essential hypertension

Sir,

With respect to the editorial comment 'Microalbuminuria in essential hypertension. A marker of systemic vascular damage?' by R. Pedrinelli [1] two comments appear to be appropriate.

1. The authors state that 'Altered glomerular permeability as a part of a systemic endothelial dysfunction ... could explain ... the appearance of microalbuminuria ...'. While this is an interesting and widely repeated hypothesis it is intriguing if presented in the way Pedrinelli proposes. By convention microalbuminuria may be diagnosed when as little as 20–40 mg of albumin are excreted in a 24-h urinary collection. However, it has been known for some time [2] that even the normal glomerulus 'filters' at least ~1000 mg of albumin per day into the proximal tubular fluid. Most of this albumin is apparently reabsorbed in the proximal tubule by a possibly active mechanism resembling receptor-mediated transport. Based on these data it is not plausible that an additional small amount of no more than 20 mg of albumin, 'filtered by a dysfunctioning' glomerulus—increasing 'filtration' from 1000 to 1020 mg per day—should be detectable in the form of a '20 mg albuminuria', when a normal kidney, filtering ~1000 mg of albumin at the glomerular level excretes next to 0 mg of albumin. Obviously something else must be going on. Since it might be important to better understand these real mechanisms of microalbuminuria, I propose that Dr Pedrinelli and his colleagues might be able to provide a more detailed and more complete explanation of the pathophysiological mechanisms of microalbuminuria.

2. Dr Pedrinelli also addresses 'the missing renal vasodilatation in response to L-arginine ... in contrast to the preserved response to acetylcholine'. Because Pedrinelli goes on to point out that L-arginine is a physiological precursor of nitric oxide he thereby implies that infused L-arginine is somehow converted to NO. He then proposes several hypotheses to put this finding into perspective with other discrepant observations concerning endothelial dysfunction in diabetic nephropathy. Surprisingly, recent work in this area [3,4] is not discussed. This recent work shows that NO-generation in response to L-arginine infusion depends—at least in part—on stimulation of insulin by L-arginine and on NO generation in response to this insulin. Because it is now known that primary 'essential' hypertension often occurs in the setting of altered insulin secretion or response to insulin—also summarized under the catchword of metabolic syndrome—the finding of L-arginine infusion as mentioned above could indeed assume a different meaning from that proposed by Pedrinelli.

Marko Gross
Universitätsklinikum Carl Gustav Carus der Technischen Universität Dresden Medizinische Klinik III — Station 10a Fetscherstrasse 74 D-01307 Dresden Germany


Reply

Sir,

Dr Gross states that ‘... it is not plausible that an additional small amount of no more than 20 mg of albumin ... should be detectable in the form of a '20 mg albuminuria' when a normal kidney, filtering approximately 1000 mg of albumin at the glomerular levels excretes next to zero mg of albumin ...'. On the contrary we find it only logical to assume that, since practically all of the filtered albumin undergoes tubular reabsorption, any even minimal additional amount of albumin leaking from the glomerulus should be retrieved in the urine. Unless one postulates some degree of tubular dysfunction, but the existing evidence is by and large, against this possibility (see for example the Editorial by Erley and Risler, Nephrol Dial Transplant, 1994; 9: 1713–1715).

As regards recent work showing that '... NO generation in response to L-arginine infusion depends—at least in part—on stimulation of insulin by L-arginine ... ', Dr Gross is certainly aware that L-Arg is not a circulating hormone but, rather, the biological intracellular precursor of nitric oxide. The work by Giugliani et al. (J Clin Invest 1997; 99: 433–446) may perhaps provide some explanation for the missing renal vasodilatation to systemic L-arginine infusion, we agree on that. However, insulin-stimulation by L-arginine has nothing to do with the vasorelaxing response to regional intra-arterial infusion of acetylcholine, which we mainly dealt with in our Editorial.

Ricercatore Universitario
Confermato
I Clinica Medica
Università di Pisa
Italy

Acute interstitial nephritis due to over-the-counter ibuprofen in a renal transplant recipient

Sir,

The differential diagnosis of acute renal transplant dysfunction includes rejection, pyelonephritis, vascular events, and ureteric obstruction. We report a case of drug-induced acute interstitial nephritis due to proprietary ibuprofen in a transplanted kidney, which illustrates the potential dangers of freely-available medication.

A 34-year-old woman with end-stage chronic renal failure...
due to IgA nephropathy received a cadaveric renal transplant (1, 1, 0 mismatch) in February 1995. The subsequent course was uneventful; she was maintained on prednisone, azathioprine, and cyclosporin and was not receiving diuretics. In May 1996 serum creatinine was 145 \( \mu \text{mol}/\text{l} \) (normal 70–140 \( \mu \text{mol}/\text{l} \)). In June 1996 she was admitted with a 1-week history of malaise, and aching and swelling of the transplant. Two to three weeks earlier she had strained her neck, and had been prescribed DF118 for pain. On admission, creatinine was 658 \( \mu \text{mol}/\text{l} \), haemoglobin 10.8 g/dl, white blood count 7.2 \( \times \text{10}^9/\text{l} \), with a normal differential. Trough monospecific cyclosporin concentration was 140 ng/ml (therapeutic range 100–200 ng/ml). Urinalysis revealed both blood and protein. Cultures of blood and urine were sterile. Doppler ultrasound of the kidney showed normal appearances, no hydronephrosis, and a normal inter-lobar resistivity index of 0.6.

Biopsy of the transplant showed normal glomeruli and blood vessels with no evidence of intimal arteritis. There was marked interstitial oedema with a diffuse inflammatory infiltrate predominantly composed of eosinophils. There was widespread tubular epithelial flattening with vacuolation of the cytoplasm of the remaining tubular cells. There was only focal tubulitis, the majority of the tubules were devoid of inflammation. In the absence of a full-blown picture of rejection and in view of the presence of large numbers of eosinophils, the most likely cause of transplant dysfunction was considered to be an acute interstitial nephritis, probably drug-related.

The patient was treated with prednisolone 60 mg daily and serum creatinine improved to 211 \( \mu \text{mol}/\text{l} \). Further questioning revealed that the prescribed analgesic had been ineffective and so she had purchased a proprietary brand of ibuprofen, which she had taken regularly up to the onset of symptoms.

Nonsteroidal anti-inflammatory drugs are well recognized as a cause of acute interstitial nephritis \([1,2]\). There are few previous reports \([3]\) of acute allergic tubulointerstitial nephritis in renal transplant patients maintained on immunosuppressive therapy, which might be presumed to be protective. Concern has been expressed over the possible adverse effects of over-the-counter preparations, although the risks are recognized as being small \([4,5]\). This case highlights the need for a full and careful drug history in all cases, with attention being paid to the increasing number of drugs which have become available as over-the-counter preparations.

Membranoproliferative glomerulonephritis associated pulmonary sarcoidosis

Sir,

Glomerulonephritis associated with sarcoidosis was first reported in 1951 when hyaline and fibrinoid changes were noted in the glomeruli of a patient with generalized sarcoidosis. Since that, numerous other histopathologic varieties of glomerulonephritis have been reported including membranous nephropathy, focal glomerulosclerosis and proliferative and membranoproliferative glomerulonephritis \([1]\). Hypercalcemia, nephrolithiasis, nephrocalcinosis, granulomatous nephritis, interstitial nephritis without sarcoid granuloma, granulomatous arteritis, glomerulonephritis are seen in renal involvement of sarcoidosis. We reported membranoproliferative glomerulonephritis in a patient with pulmonary sarcoidosis. Prednisolone therapy caused resolution of nephrotic syndrome and pulmonary lesions.

A 37-year-old man was admitted to hospital for exertional dispne and oedema. Past history revealed headache, hypertension, and oedema. Physical examination disclosed blood pressure 190/100 mmHg, pretibial oedema, and rales on the lungs. Abnormal laboratory findings were as follows: haemacrit 32.6%, haemoglobin 9.5 g/dl, white blood cells 11900/mm\(^3\), total protein 8.4 g/dl, albumin 3.5 g/dl, cholesterol 249 mg/dl, HDL cholesterol 84 mg/dl, LDL cholesterol 142 mg/dl, serum Ca 9.9 mg/dl. Antinuclear antibody, rheumatoid factor, hepatitis markers for hepatitis A, B, and C were negative. PPD was negative. Daily proteinuria was 2.5 g. Chest X-ray film and CT scan of the chest showed mediastinal and bilateral hilar lymphadenopathy and an increase in density of the lung parenchyma. Respiratory function tests showed restrictive changes. Rectal and bone marrow biopsies and subcutaneous fat aspiration did not contain deposition of amyloidosis. Noncaseating granulomatous inflammation was found in bronchial mucosa obtained by fiberoptic bronchoscopy. Renal biopsy showed membranoproliferative glomerulonephritis (Figure 1). Deposition of amyloidosis was negative. T4 and T8 were 36% and 23.8%, respectively. NBT was 10%. Serum thyroid hormone levels were normal. Serum angiotensin converting enzyme (ACE) level was 10 U. The patient was treated with prednisolone 1 mg/kg/day, famotidin 20 mg/day, and amlodipin 5 mg/day.


Fig. 1. Light microscopic examination (H & E \( \times 375 \)) showed: expansion of glomerular tuft, increment of cellularity and mesangial matrix, thickening basement membrane, infiltration of polymorphonuclear leucocytes (PMN) and mixed infiltration including PMN of the interstitium.