RENAL MEDICINE

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This biennial meeting in renal medicine included speakers from throughout the UK and, for the Davidson Lecture, from Indianapolis. The symposium examined our understanding of the complex relationship between renal dysfunction and cardiovascular disease, extending from the laboratory and basic science through to its application in clinical practice.

The young patient with renal failure suffers an excess mortality 100 times that of the aged matched population, with the majority of that risk attributable to accelerated cardiovascular disease. Conversely, with an ageing population, renal dysfunction secondary to the effects of systemic arteriosclerosis represents a significant and increasing burden on renal services and dialysis resources. Our understanding of how such diseases are optimally managed in both primary and secondary prevention is far from complete, and lags behind the progress made in addressing the cardiac and cerebral manifestations of vascular disease in the non-uraemic population.

The morning session opened with Dr Scoble (Guy's, King's and Thomas' NHS Trust, London, England) discussing 'Disease of the renal vasculature: aetiology and management'. Experience from live donor programmes suggests the prevalence of renovascular disease is 4–7% in an otherwise healthy, normotensive population. Additionally, in young patients the antiphospholipid syndrome has recently been recognised as a potential underlying cause, due to thrombosis and subsequent recanalisation. When screening patients on haemodialysis, the prevalence of renal artery stenosis which is severe enough to contribute to renal failure was 14%, even in those with other renal diagnoses. Thus, renovascular disease is likely to account for a substantial and potentially increasing proportion of end-stage renal disease (ESRD), and the optimal management of its early stages is not yet clear. Prospective randomised controlled trial data is required, and the ongoing ASTRAL study should go some way to establishing the role of renal angioplasty in maintaining renal function.

Dr Goldsmith (Guy's Hospital, London, England) spoke about 'Cardiac disease in uraemia'. He highlighted the huge excess of cardiac disease in patients with chronic renal failure. Two critical features of cardiovascular disease in renal failure are coronary and peripheral artery calcification, and left ventricular hypertrophy (LVH). The changes of LVH can occur early in the natural history of disease, even with a normal creatinine clearance. The nature of the cardiac disease is unusual, with myocardial fibrosis a prominent finding. Classically, medial calcification occurs in the coronary arteries, without the inflammation and lipid deposition characteristic of occlusive atherosclerotic disease. Thus the applicability of secondary prevention strategies validated in the non-uraemic population must be questioned. Better regulation of calcium homeostasis and control of anaemia and intravascular volume shifts may be of relevance in altering the evolution of these disease states.

The difficulties of extrapolating general population data to uraemic patients was explored by Dr Wheeler (Royal Free Hospital, London, England) in his talk 'Lipid disorders in chronic kidney disease'. Whilst hyperlipidaemia is a recognised cardiac risk factor in the general population, there is a paucity of data to support this in renal disease. In dialysis patients there is an excess mortality risk with low cholesterol levels, but no apparent risk increase at high levels. This may reflect the different aetiology of the vascular disease in this population. The ALERT study which looked at the use of statins in hyper-cholesterolaemic patients after renal transplantation failed to show any reduction in total mortality, although cardiac death was reduced. Whether aggressive lipid lowering is of benefit in chronic renal disease and ESRD will hopefully be answered by the ongoing Study of Heart and Renal Protection (SHARP) study, using a dual agent strategy to reduce low-density lipoprotein.

There was a synergy between the themes of Professor Cunningham (Middlesex Hospital, London, England) and the Davidson lecturer, Dr Moe (Indiana University School of Medicine, Indiana, US). Professor Cunningham spoke on the challenge of controlling calcium and phosphate balance in the dialysis patient. Having a high calcium x phosphorus (Ca x P) product is a risk factor for mortality on dialysis. In the UK, calcium-containing phosphate binders are the mainstay of therapy, but themselves may contribute to the calcium burden. Exciting new tools are becoming available, with calcium-free binding agents, and the arrival of 'calcimimetics' – agents which activate the calcium receptors of the parathyroid gland, triggering negative feedback with potent suppression of parathyroid hormone (PTH). Whether these new tools will allow us to meet higher standards of both serum and bone biochemistry, and improve vascular outcomes remains to be evaluated.

Dr Moe reviewed the recent work advancing

understanding of the mechanisms by which ectopic vascular calcification occurs in renal disease. There is emerging evidence that calcification levels present in the coronary arteries of the general population can act as an additional prognostic tool in ischaemic heart disease. When one assesses coronary calcification in the dialysis population, there is an exponential increase in calcium burden, even compared to a non-uraemic population with three-vessel coronary disease. Predisposing factors include increasing time spent on dialysis, age, and, again, a raised Ca x P product. *In vitro* evidence suggests that vascular smooth muscle can develop into osteoblast-like cells which lay down bone-type extra-cellular matrix. Further studies have suggested that hyperphosphataemic serum can promote this process, as can a low blood PTH concentration. This adds weight to current arguments that over-control of PTH with resultant suppression of bone turnover is undesirable. It appears that in the dialysis population the combination of high calcium and phosphate delivery, and abnormalities in the skeleton's ability to buffer calcium may all combine to promote the deposition of extra-osseous calcium.

The afternoon session examined advances in the understanding and management of diabetic renal disease. Professor Marshall (University of Newcastle-upon-Tyne, England) examined the role of the podocyte in the pathogenesis of diabetic nephropathy (DN). Her research suggested that progressive loss of podocytes is an early finding in DN, and is present even in those yet to exhibit detectable albuminuria. An additional finding is that Angiotensin II (AT-II) inhibits the Nephrin gene, a vital component for the integrity of the podocyte slit membrane. Agents that block AT-II action have been shown to improve proteinuria and outcome in DN, and one such agent, Irbesartan, increases Nephrin expression in an *in vitro* model. Additional *in vitro* work attempted to recreate the mechanical stresses placed on podocytes *in vitro*, showing that the addition of a hyperglycaemic serum significantly reduced their adhesion characteristics. These findings start to delineate the pathogenesis behind the population observations of worsening DN in those with poor glycaemic and hypertensive control.

Two surgeons from the Transplant Unit of the Royal Infirmary of Edinburgh spoke on the emerging role of pancreatic transplantation for diabetes mellitus. Mr Akyol outlined some of the surgical approaches used. Simultaneous pancreatic and kidney transplantation (SPK) appears to confer benefits in graft survival over both isolated pancreas and pancreas-after-kidney transplant. Whilst a prospective randomised controlled trial of SPK versus kidney-alone transplant in diabetes has never been done, retrospective analysis of diabetics on the same transplant list receiving both organs rather than one suggests a higher five-year survival rate. Experience also suggests that after SPK neuropathy and retinopathy can stabilise, and the renal graft should be protected from recurrent nephropathy.

One of the disadvantages of organ transplant surgery is the morbidity and mortality entailed by such a large procedure in a high-risk patient. Mr Casey outlined the progress being made in pancreatic islet cell transplantation. This technique offers the hope of an effective 'cure' for diabetes that can be administered via a day case radiological procedure, rather than major abdominal surgery. Early attempts worldwide had failed to achieve successful engraftment and insulin independence, however, the Edmonton group (acknowledged leaders in this field) has pioneered a corticosteroid-free engraftment regime, with over 60 successful recipients. Work is now at an advanced stage to offer islet cell transplantation to the Scottish population.

Completing our examination of the vasculature in renal disease, Professor Webb (Western General Hospital, Edinburgh, Scotland) spoke on endothelial dysfunction in chronic renal failure, and the putative therapeutic interventions under investigation. It is recognised that the endothelium behaves differently in patients with hypertension and with renal failure, compared with the general population. Production and response to endogenous vasodilators such as Nitric Oxide are reduced, whilst agents such as Endothelin-1 exert a deleterious effect on the microcirculation. Measurement of arterial stiffness and resultant arterial pulse wave velocity is validated as an additional marker of vascular risk, in addition to more traditional factors such as blood pressure and lipids. Recent work in Edinburgh has identified antagonism of the Endothelin A receptor as a promising therapy in chronic renal disease. This appears to act synergistically with ACE inhibition, resulting in systemic blood pressure and renal vascular resistance, whilst increasing renal blood flow and fractional sodium excretion.

Professor Poston (Guy's, King's and St Thomas' Hospital, London, England) concluded the day with a review of one of the major causes of maternal and fetal morbidity and mortality, pre-eclampsia (PE). Patients with pre-existing renal impairment are at markedly increased risk of developing PE, and her group's work suggests that changes in endothelial function precede the initiation of the clinical syndrome. Increased oxidative stress has been implicated as a potential mechanism driving the maternal circulatory changes. Most excitingly, in a preliminary trial, the administration of oral antioxidant vitamins C and E resulted in a fourfold reduction in PE in those completing the study.

Professor Poston's lecture provided an elegant illustration of advances in the understanding of the basic science of disease guiding therapeutics, and a fitting end to a most stimulating day of education. The lively debate and questions, from physicians in a range of specialties illustrated the broad appeal of the topics covered.