ABSTRACTS: RENAL MEDICINE

1 June 2004

SESSION 1
VASCULAR DISEASE AND THE KIDNEY

Chair: Professor DJ Webb, Christison Professor of Therapeutics and Clinical Pharmacology, University of Edinburgh, Edinburgh, Scotland

DISEASE OF THE RENAL VASCULATURE: AETIOLOGY AND MANAGEMENT

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Abstract

Renovascular disease can be caused by a number of pathologies. Common to all of these is the change produced in renal blood flow. The clinical outcome, however, depends on the pathological process producing the narrowing. The outcomes from Takayasu's disease and middle aortic syndrome are very different even though both affect the renal ostium and spare the intra-renal vessels. New data from assessments of living donors have suggested that fibromuscular dysplasia (FMD) is present in 5% of healthy normotensive individuals in the community. The most common cause of renovascular disease is atherosclerotic renal artery stenosis. The importance of this as a cause of end-stage renal failure has been increasing. However, the therapeutic options are less clear.

Randomised controlled trials (RCTs) of intervention in renal artery stenosis have shown a number of features. These have looked at patency of the renal artery and blood pressure control. There are a number of anecdotal single-centre experiences of intervention to alter function but no RCTs. At present there are four RCTs in progress and none of them has reported their results. The Angioplasty and STent for Renal Artery Lesions (ASTRAL) trial is the largest and has recruited over 300 patients.

Renal artery stent insertion has been shown to provide better patency than angioplasty alone. Randomised controlled trials have not shown an improvement in blood pressure control with angioplasty in atherosclerotic disease but do in FMD. Observational studies have suggested methods of predicting which patient's renal function will benefit from angioplasty but these are not randomised.

Management of certain forms of renovascular disease such as FMD or Takayasu's disease is clear. However, for the most common form secondary to atherosclerotic disease no evidence exists for best practice based on RCT data.

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Key words: atherosclerotic renal artery stenosis, fibromuscular dysplasia.

Sponsors: None.

Declaration: No conflict of interest declared.

CARDIAC DISEASE IN URAEMIA

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Abstract: Not available at the time of going to press.

LIPID DISORDERS IN CHRONIC KIDNEY DISEASE

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Abstract: Not available at the time of going to press.

SESSION 2
CALCIUM AND THE KIDNEY

Chair: Dr RJ Winney, Consultant Renal Physician, Royal Infirmary of Edinburgh, Edinburgh, Scotland

OSTEODYSTROPHY – HOW TO KEEP CALCIUM IN THE BONES AND AWAY FROM THE ARTERIES

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Abstract

Patients with chronic kidney disease (CKD) experience:

1. High general and cardiovascular mortality rates.
2. A progressive osteodystrophy, variably comprising hyperparathyroidism with hyperparathyroid bone disease and relative hypoparathyroidism with low turnover adynamic bone disease.
3. Extensive medial calcification of the arteries and other soft tissue calcification.

Increasingly, research directed at understanding the pathogenesis and pathophysiology of renal osteodystrophy has pointed towards links with the cardiovascular system and via this with cardiovascular morbidity, mortality and calcification.

Current treatments for renal osteodystrophy centre around prevention of hyperphosphataemia (using a combination of adequate dialysis prescription, dietary phosphate restriction and oral phosphate binders), together with treatment of secondary hyperparathyroidism using active 1-hydroxylated metabolites of vitamin D. It has become apparent that these therapies, particularly if the phosphate binding regime uses large doses of calcium salts, are associated with progressive and substantial calcium loading of uraemic patients and that this is a contributory factor to the extensive vascular and other soft tissue calcification experienced. Important new measures that may reduce calcium loading include a switch to calcium-free phosphate binders, a number of which have recently, or will shortly, enter the clinical arena. Calcimimetic agents, which are capable of reducing simultaneously parathyroid hormone, calcium, phosphate and the calcium x phosphorus (Ca x P) product, increase the proportion of patients achieving current therapeutic targets for these variables, reduce excessive calcium loading and may reduce vascular and other soft tissue calcification in uraemia. It remains to be seen whether these new treatments improve skeletal, metabolic and cardiovascular outcomes in uraemia.

The evolving strategies for the treatment of renal osteodystrophy may in the past have contributed to accelerated soft tissue and vascular calcification. The newest approaches, using a combination of calcium-free phosphate binders and calcimimetic agents, have already improved the level of attainment of therapeutic targets, and may lead to an important reduction of calcium loading, soft tissue calcification, and possibly cardiovascular morbidity and mortality.

Key words: calcimimetics, calcium-free phosphate binders, chronic kidney disease, hyperparathyroidism, renal osteodystrophy, vascular calcification.

Sponsors: None.

Declaration: Paid consultant to Genzyme, Amgen and Abbott.

THE DAVIDSON LECTURE

Chair: Dr RH Smith, Vice-President, Royal College of Physicians of Edinburgh, Edinburgh, Scotland

VASCULAR CALCIFICATION

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Abstract

Cardiovascular disease is the leading cause of death in patients undergoing dialysis.[1] Analysis of the recent Hemodialysis (HEMO) trial indicated that 15% of the cardiovascular disease observed in CKD cannot be explained by the traditional risk factors of diabetes, hypertension, family history, hyperlipidemia and smoking,[2] leading to the notion that there are dialysis-specific cardiovascular risk factors. In addition, there is now increasing evidence that alteration in mineral metabolism may also play a role in cardiovascular disease in CKD.

The observation that calcification, or mineralisation, can occur in arteries is not new. Work done by Stary *et al.*, using monkey models of hypercholesterolemia, and autopsy specimens noted that calcification in atherosclerotic (intimal plaque) disease was frequently calcified, although this occurred very late in the progression of these lesions.[3] In addition, another form of calcification located only in the medial layer of the artery, Mönckeberg calcification, has been observed for some time, especially in the distal vessels of diabetics and patients with CKD.[4] Yet another form of arterial calcification, calciphylaxis, has been observed. Thus, calcification can occur in intimal or atherosclerotic disease, and in the medial layer of all forms of arteries.

Due to the variety of locations of calcification in arteries, it was initially felt that the calcification represented an artifact of serum supersaturation for calcium and phosphate (which is obviously increased in renal failure), and thus a passive deposition. However, recent evidence supports that this is a complex, regulated process that appears to be accelerated in patients with CKD.

Ibels *et al.,* in 1979,[5] demonstrated that both renal and internal iliac arteries of patients undergoing a renal transplant had increased atherogenic/intimal disease and increased calcification (detected by chemical methods) compared to transplant donors. In addition, the medial layer was thicker and more calcified in the uraemic patients compared to the donors.[5] A more recent study evaluated coronary arteries obtained at autopsy in dialysis patients compared to age matched, non-dialysis patients who had died from a cardiac event.[6] This study found a similar magnitude of atherosclerotic disease, but that it was more heavily calcified in dialysis patients. In addition, morphometry of the arteries demonstrated increased medial thickening,[6] although calcification in the medial layer did not appear to be increased, it was also not specifically evaluated (K Amann, personal communication). Thus, there is histological evidence for increased arterial calcification in patients on dialysis compared to non-dialysis patients.

Clinically, arterial calcification can be detected through a number of techniques including visualisation of plain radiographs, tomography, scintigraphy and computerised tomography (CT) scan. The latter, initially developed as electron beam CT scan, was devised only to evaluate coronary artery calcification with speeds to scan in diastole only, in order to avoid motion artifact. Thus, the scanner is linked to the ECG tracing, and images only obtained during diastole. Evolution of the spiral CT scanners has also allowed rapid acquisition of images. Two techniques for gating to ECG tracings exist, including retrospective and prospective. The latter is similar to electron beam computed tomography (EBCT), and in retrospective it is done by taking images all through the cardiac cycle and then retrospectively using only the images in diastole. While there is some distinct appearance to medial compared to intimal calcification on plain radiographs,[7] neither EBCT nor spiral CT can differentiate intimal from medial calcification.

Braun *et al*.[8] demonstrated that coronary artery calcification by EBCT increased with advancing age in patients on dialysis and that the calcification scores[8] were two to fivefold greater in dialysis patients than age matched individuals with normal renal function and angiographically proven coronary artery disease. Goodman *et al*.[9] subsequently demonstrated that advanced calcification can also occur in the coronary arteries of children and young adults and found a relationship between increasing doses of calcium containing phosphate binders, increased Ca x P product and increasing calcification scores. We subsequently demonstrated that spiral CT with retrospective gating (described above) can also detect coronary artery calcification.[10] Several other authors have reported vascular calcification using these various techniques, and have determined the risk factors associated with the presence or absence of calcification or the degree of calcification. The only risk factors that are uniform across studies are advancing age, and duration of dialysis. Mineral metabolism abnormalities in the form of elevated phosphorus, elevated Ca x P, or calcium load in the form of phosphate binders are not uniformly identified risk factors.

To date, there are no published data clearly demonstrating adverse cardiac outcomes with coronary artery calcification in end-stage renal disease (ESRD) patients, although this has been demonstrated in the general population. Recently, London *et al*.[7] evaluated a large cohort of dialysis patients with plain radiography of the pelvis and thigh and differentiated between intimal calcification, and medial alone or medial plus intimal calcification. There was an increased mortality risk in patients with vascular calcification in an intimal pattern compared to a medial pattern, but in turn the mortality was still greater than patients with no calcification. Thus, there is increasing evidence that vascular calcification is indeed associated with morbidity and mortality, regardless of the imaging technique and regardless of the location.

To examine the pathophysiology of vascular calcification observed in dialysis patients, we examined arteries histologically.[11, 12] We have found expression of bone proteins in calcified arteries from patients with calcific uraemic arteriolopathy, and in the inferior epigastric arteries from patients with ESRD undergoing renal transplantation.[12] The presence of positive immunostaining for these bone proteins was found more frequently than was overt calcification, which suggests that the deposition of these proteins precedes calcification. Thus, our *ex vivo* findings suggest that the initial changes that occur in the vessels of dialysis patients are the deposition of these bone matrix proteins, followed by calcification. Further studies have demonstrated the presence of Cbfa1, a bone specific transcription factor, which is upregulated in vascular smooth muscle cells incubated with serum from uraemic patients compared to non-dialysis patients, and is expressed *in vivo* in arteries in areas with calcification.[13] Thus, there is clear evidence for a regulated mechanism of vascular calcification that parallels bone formation. In addition, there appears to be naturally occurring inhibitors such as fetuin-A, a circulating factor, and matrix Gla protein expressed locally that may serve to inhibit vascular calcification.[14]

In conclusion, we hypothesise that vascular calcification in dialysis patients may be a three-step process. First, vascular smooth muscle cells are stimulated by uraemic toxins, including phosphorus leading to transformation into osteoblast-like cells. Whether expression of Cbfa1 is critical for the de-differentiation or is simply a marker of de-differentiation remains unknown. These bone-like cells in arteries then lay down a bone matrix of type I collagen and non-collagenous proteins. The final step may be mineralisation of this matrix, in part through a physiochemical process and in part through a process 'guided' by the matrix proteins and osteoblast-like cells. This latter step is likely to be a balance of excess mineral load and inhibitors.

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Key words: arterial calcification, bone specific transcription factor, calcific uraemic arteriolopathy, calciphylaxis, Cbfa1, dialysis specific cardiovascular risk factors, fetuin-A, matrix Gla protein, Mönckeberg calcification.

Sponsors: None.

Declaration: No conflict of interest declared.

SESSION 3
DIABETES MELLITUS AND THE KIDNEY

Chair: Dr JD Walker, Consultant Physician, St John's Hospital, Livingston, Scotland

DIABETIC NEPHROPATHY

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Abstract

It is generally believed that the increased urine albumin excretion in diabetic nephropathy is mostly glomerular in origin. For albumin to appear in the urine it must cross the glomerular filtration barrier, which consists of fenestrated glomerular endothelial cells, the glomerular basement membrane and the glomerular epithelial cell or podocyte. It has long been appreciated that increased intra-glomerular pressure, loss of negatively charged glycosaminoglycans in the basement membrane and, later in the disease process, increased basement membrane pore size, all contribute to the albuminuria. Well-described microscopic abnormalities include thickening of the glomerular basement membrane, accumulation of mesangial matrix and increased numbers of mesangial cells. As the disease advances, there is a close relationship between mesangial expansion and declining glomerular filtration (GFR). Mesangial expansion also correlates inversely with capillary-filtration surface area, which itself correlates to GFR.

Recently, it has been demonstrated that the podocyte may also have a role in increasing proteinuria and developing glomerulosclerosis. The podocyte is a terminally differentiated epithelial cell with a cell body from which numerous processes branch.[1] These processes divide successively until the terminal foot process rests on the glomerular basement membrane. Foot processes interdigitate so that neighbouring foot processes are from different podocytes. The podocyte, via the foot processes, provides structural support for the glomerular capillaries, buffers intraglomerular pressure and is the final layer in the barrier to protein

passage across the glomerulus into the urinary space. Like the basement membrane, the podocyte is covered by negatively charged molecules which help repel anionic proteins such as albumin. In addition, the negative charge helps keep open the slit diaphragm, the structure which bridges the gap between adjacent foot processes. The slit diaphragm is essential in preventing proteinuria, slit diaphragm proteins such as nephrin having an essential role in preventing escape of protein into Bowman's space.

In both human and experimental diabetes, podocyte morphology is abnormal. The foot processes broaden and efface. Eventually there is loss of the podocyte itself. Podocytes cannot regenerate so this loss cannot be compensated for. There is also decreased expression of nephrin mRNA and protein.[2] Abnormalities in several podocyte proteins have been demonstrated to cause proteinuric renal diseases in humans, for example: absence of nephrin in Finnish congenital nephritic syndrome; CD2-adaptor protein and podocin in forms of steroid-resistant nephritic syndrome.

Thus it is possible that podocyte protein abnormalities in diabetes contribute to proteinuria and eventual glomerulosclerosis. Whether these are primary abnormalities in the development of proteinuria in diabetes, or occur later in the disease process is currently a matter of some controversy.[3, 4]

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Key words: diabetic nephropathy, intraglomerular pressure, nephrin, podocyte, podocyte foot process, proteinuria, renal haemodynamics.

Sponsors: Professor of Diabetes, University of Newcastle upon Tyne; Consultant Physician, Newcastle upon Tyne Acute Hospitals NHS Trust and Newcastle upon Tyne Primary Care Trust.

Declaration: I have received grants for specific research studies and speaker fees from a number of pharmaceutical companies.

KIDNEY – PANCREAS TRANSPLANTATION

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Abstract

Pancreas transplantation is the only treatment available that reliably offers normoglycaemia independent of insulin for patients with Type 1 diabetes mellitus. It has been described in the early 1960s, earlier than all other solid organ transplants except kidney transplantation. It is only in the last 10–12 years that the success rate with this procedure has become comparable to that achieved with other forms of transplantation.[1] More than 20,000 pancreas transplants have been performed worldwide.[2, 3] A national pancreas transplantation service for Scotland has been established at the Royal Infirmary of Edinburgh since April 2000.

The clinical settings in which pancreas transplantation is performed and some recent developments in patient selection, surgery and post-operative management will be reviewed. Recent data with respect to the influence of pancreas transplantation on diabetic complications and life-expectancy will also be discussed.

Pancreas transplantation has never been compared with insulin therapy in the management of patients with Type 1 diabetes in a controlled trial. There is nevertheless increasing evidence from other studies and databases[2, 3] that it is now a successful and safe procedure with considerable potential benefits for selected patients with Type 1 diabetes.

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Key words: diabetes mellitus, kidney transplantation, pancreas transplantation.

Sponsors: None.

Declaration: No conflict of interest declared.

ISLET CELL TRANSPLANTATION

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Abstract: Not available at the time of going to press.

SESSION 4
ENDOTHELIAL DYSFUNCTION IN HEALTH AND DISEASE

Chair: Dr WA Liston, Consultant Obstetrician and Gynaecologist, Royal Infirmary of Edinburgh, Edinburgh, Scotland

ENDOTHELIAL FUNCTION IN HEALTH AND DISEASE

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Abstract

Chronic kidney (renal) disease is a worldwide public health problem, with poor outcomes and a high healthcare cost. Although chronic renal failure (CRF), leading to dialysis and transplantation, may be the most visible aspect of kidney disease, many patients with renal disease develop hypertension and the majority die prematurely of cardiovascular disease.[1] The normal function of the endothelium, the cells lining blood vessels, and the compliance of arteries, appear to be important determinants of cardiovascular health. However, the endothelium is dysfunctional and arteries stiffen in CRF, and these factors may contribute to hypertension, atherosclerosis and the burden of cardiovascular disease, in this condition.[2]

There is evidence that the endothelin (ET) system is overactive and that the nitric oxide (NO) system functions poorly in CRF. Cytokines may drive ET activation and a combination of hypertension, oxidative stress and retention of NO synthesis inhibitors, including asymmetric dimethylarginine, may reduce NO bioactivity.[3,4] This endothelial dysfunction promotes vasoconstriction, cardiovascular remodelling, inflammation and thrombosis. Endothelin antagonists not only block ET actions, but also improve NO function and unstiffen arteries. Clinically, in addition to angiotensin-converting enzyme inhibition, they lower blood pressure while producing renal effects that may be 'renoprotective'.[5,6]

Endothelial dysfunction and arterial stiffness may be important markers of cardiovascular risk and restoration of endothelial function may be an important future therapeutic target in CRF patients. Therapeutic approaches may include endothelin antagonism, phosphodiesterase type 5 inhibition and cyclic guanosine monophosphate activation/stimulation.

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Key words: arterial compliance, blood pressure, endothelial function, endothelin, endothelium, nitric oxide, proteinuria, renoprotection, vascular tone.

Sponsors: None.

Declaration: The author has no specific conflicts of interest in this talk, but has in the past given advice to a number of pharmaceutical companies in relation to therapeutic approaches to reversal of endothelial dysfunction.

ENDOTHELIAL FUNCTION IN PRE-ECLAMPSIA

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Abstract

Pre-eclampsia occurs in approximately 4% of all pregnancies but the risk increases in women with renal disease and is influenced by the degree of renal impairment, the severity of accompanying hypertension, the degree of proteinuria and the type of renal disease. Endothelial cell activation and impaired endothelium-dependent relaxation are now regarded as central to the aetiology of pre-eclampsia and may be a consequence of placental and maternal oxidant stress.[1–4]

Early work from our laboratory showed impairment of

endothelium-dependent relaxation in isolated small arteries from women with pre-eclampsia. Others have found increased plasma concentrations of soluble cell adhesion molecules, endothelin, PAI-1 and other markers of endothelial cell activation. Recent studies using venous occlusion plethysmography have shown reduced blood flow in association with increased endothelial permeability in the peripheral circulation. Synthesis of superoxide is enhanced in the pre-eclamptic placenta and markers of lipid peroxidation are evident.[1] Current theory suggests that ischaemia/reperfusion in the placenta leads to free radical synthesis, generation of cytokines, microparticle deportation and activation of maternal neutrophils which together result in exaggeration of the normal inflammatory response to pregnancy and maternal oxidant stress.[2–4] This theory is supported by a small RCT in which we showed reduced occurrence of pre-eclampsia in women at risk randomised to supplements of vitamin C and E.[5]

Pre-eclampsia shares many of the characteristics of CRF and these commonalities may underlie the increased risk of pre-eclampsia in renal disease. Several large multicentre trials now underway will determine whether antioxidant supplements may be an effective intervention for the prevention of this common disorder.

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Key words: endothelium, inflammatory response, oxidative stress, pre-eclampsia.

Sponsors: The Wellcome Trust, Tommy's the Baby Charity.

Declaration: The author has no conflicts of interest.