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Renal Medicine Symposium Report

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ABSTRACT This renal symposium provided an overview of diverse but key areas of nephrology. Topics included the molecular basis of the glomerular filtration barrier; the clinical management of the nephrotic syndrome; the association of CKD with cardiovascular morbidity; the link between hyperuricaemia, obesity and cardiovascular disease; current immunosuppressive therapies; long-term morbidity and mortality issues in transplant recipients; electrolyte disorders; and conservative therapy for renal failure.

KEYWORDS Arterial stiffness, chronic allograft nephropathy, conservative therapy, oroteinuria, uric acid

LIST OF ABBREVIATIONS Angiotensin converting enzyme (ACE), chronic allograft nephropathy (CAN), chronic kidney disease (CKD), glomerular basement membrane (GBM), electrocardiograph (ECG), end-stage renal disease (ESRD), focal segmental glomerulosclerosis (FSGS), mammalian target of rapamycin (mTOR), matrix metalloproteinase 9 (MMP9), peroxisome proliferator activated receptor gamma (PPARγ), vascular endothelial growth factor (VEGF)

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SESSION 1
PROTEINURIA AND NEPHROTIC SYNDROME

Dr M Saleem, Dr N Brunskill, and Professor P Mathieson

Dr Saleem, Bristol Royal Hospital for Children, outlined the composition of the glomerular filtration barrier which consists of the GBM sandwiched between the inner fenestrated glomerular endothelial cells and the outer podocytes. Mutations of several podocyte proteins including nephrin, podocin, CD2AP, α-actinin-4 and TRPC6 have been found in congenital and familial nephrotic syndromes. These proteins are linked dynamically through their interactions with the actin cytoskeleton and intracellular signalling cascades. Nephrin, podocin and CD2AP are complexed in lipid rafts that form an intrinsic part of the intracellular signalling cascade. Podocytes utilise α3β1-integrin and other receptors to attach to the GBM. The importance of this interaction was highlighted by the discovery of a human β2-laminin mutation that leads to early onset nephrotic syndrome (Pierson syndrome). Recent work has also highlighted the importance of podocyte-derived VEGF and its antagonist Ang-1 in inducing capillary loop formation and stabilising the phenotype of the fenestrated glomerular endothelium.[1] Experimental studies have examined the effect of human plasma from FSGS patients in remission or relapse upon the permeability of monolayers of human immortalised podocytes *in vitro*. These suggest that normal human plasma actively maintains the morphology of the slit diaphragm via inhibition of the signalling molecule RhoA and subsequent modulation of the cytoskeleton. This work may provide novel therapeutic targets for patients affected by FSGS.

Dr Brunskill, Department of Nephrology, Leicester General Hospital, outlined the 'proteinuric nephropathy' hypothesis that highlights the idea that filtered proteins induce tubular cell damage and ultimately tubulointerstitial fibrosis. Supportive evidence includes better correlation of creatinine clearance with histological tubulointerstitial damage than glomerular disease. Experimental work indicates that protein endocytosed by tubular cells activates signalling pathways that induce the release of mediators that promote tubulointerstitial scarring. Elegant experiments utilised the anatomically unusual Axolotl kidney which drains into the peritoneal cavity to demonstrate independence of renal scarring from glomerular injury since administration of excess protein into the peritoneum induced renal fibrosis in the absence of any glomerular pathology.[2] Furthermore, a rat model of protein-overload nephrosis indicated that fatty acids associated with albumin augment renal inflammation through activation of PPARγ.[3] Reduced proteinuria is associated with a slower decline of renal function in both diabetic and non-diabetic proteinuric patients. There is no current randomised control trial evidence indicating a renoprotective effect of lipid reduction, with a meta-analysis of small trials showing only a mild benefit. However, 'statins' reduce proximal tubular cell albumin endocytosis and re-absorption,[4] whilst agents such as thiazolidinediones reduce albumin endocytosis

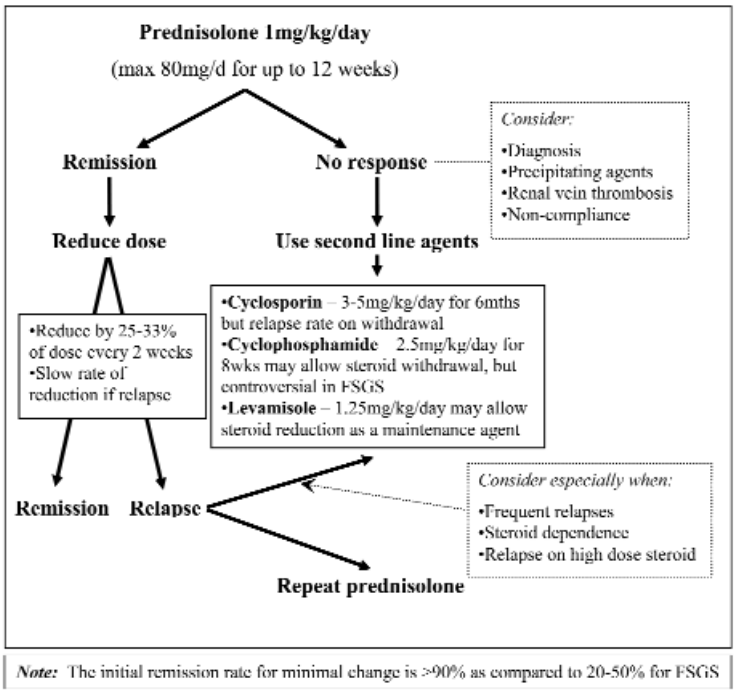

FIGURE 1 A treatment algorithm for minimal change disease and FSGS.

by proximal tubular cells.[5] Thiazolidinediones have been shown to reduce proteinuria in diabetic renal disease and are currently being assessed in non-diabetic proteinuric states.

Professor Mathieson, Academic Renal Unit, Southmead Hospital, Bristol, reviewed the clinical management of nephrotic syndrome, the clinical triad of oedema, proteinuria and hypoalbuminaemia associated with hyperlipidaemia and hypercoagulability. Interestingly, the reason why the 'nephrotic kidney' retains salt and water remains unclear. The classical theory involving activation of the renin angiotensin aldosterone system has been questioned, with recent work suggesting increased sodium uptake by the tubular cells.[6] The importance of blood pressure control in preventing the progression of renal disease and reducing proteinuria was highlighted, although ACE inhibitors may have an additional benefit. Prophylactic anti-coagulation should be considered in severely nephrotic patients and is merited in membranous glomerulonephritis when the serum albumin falls below 20 g/l. Further management of nephrotic syndrome involves the treatment of the underlying condition such as diabetes, amyloid and infectious agents.

The pathogenic aetiology of nephrotic syndrome is changing, with an increase in the proportion of cases due to FSGS. Although there is a little evidence-base in adults, a treatment algorithm was presented for FSGS and minimal change nephropathy (see Figure 1) including the importance of reducing collateral damage from steroids through gastric and bone protection. Regarding membranous nephropathy, the importance of seeking an underlying cause was stressed in terms of drugs, infectious agents and malignancy. Although steroids alone remain ineffective, evidence-based practice is still being gathered. Newer agents are on the horizon that link into the molecular mechanisms outlined in the initial talk e.g. Rho kinase inhibitors such as fluvastatin and fasudil.

SESSION 2
HYPERTENSION AND RENAL DISEASE

Dr I Wilkinson and Professor R Johnson

Dr Wilkinson, Vascular Research Clinics, Addenbrooke's Hospital, Cambridge, highlighted the increased cardiovascular risk in patients with CKD and stressed the importance of arterial stiffness. Aortic stiffness increases with deteriorating renal function, is exacerbated by hypertension[7] and is associated with increasing cardiovascular mortality in the context of ESRD.[8] The pathogenesis of arterial stiffness in ESRD probably involves several mechanisms:

- Age-related 'fatigue fractures' of elastic fibres exacerbated by for example genetic predisposition, diabetes and smoking;
- Accelerated arterial calcification that results in a release of factors such as MMP9 leading to elastin degradation;
- Impairment of endothelial nitric oxide formation.

Although current anti-hypertensive therapies have similar indirect effects on arterial stiffness, nitric oxide donors in the form of nitrates reduce arterial stiffness and systolic blood pressure.[9] Renal transplantation also reduces arterial stiffness.[10] New agents that directly affect arterial

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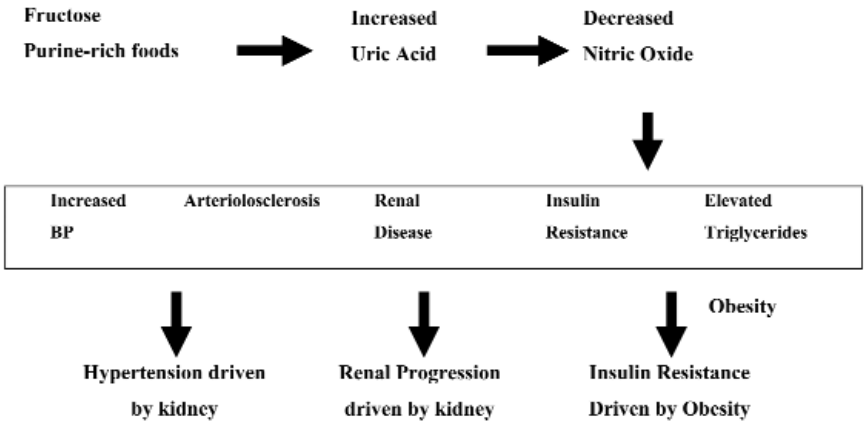

FIGURE 2 The postulated association between fructose, hyperuricaemia and the epidemic of obesity and cardiovascular disease.

stiffness are under development, for example the collagen cross-link breaker ALT-711.

Professor Johnson, Chief of Nephrology, Hypertension and Renal Transplantation, Department of Medicine, University of Florida, in his Sir Stanley Davidson lecture postulated a crucial role for fructose and uric acid in the current epidemic of obesity and cardiovascular disease. It is only in the last decade that the role of uric acid as an independent predictor of hypertension has been confirmed. Recent work in Professor Johnson's laboratory used the hyperuricaemic rat model to demonstrate the association between hyperuricaemia and hypertension, and suggested that reduced endothelial nitric oxide expression and increased vascular smooth muscle cell proliferation resulted in pre-glomerular microvascular lesions similar to those first described by Goldblatt in 1947.[11] Further work has shown two phases of hypertension: an early uric acid-dependent phase followed by a late salt-sensitive phase where there is renal arteriosclerosis.[12] Although there is preliminary data demonstrating a slowing of renal disease progression in a small group of patients treated with allopurinol, larger randomised studies are awaited.

Professor Johnson then outlined the possible detrimental effect of fructose in relation to both obesity and hyperuricaemia. Fructose is associated with obesity in rat models, is the only sugar associated with an increase in uric acid levels that can induce a diabetic phenotype, and upregulates its own enzyme system, thereby compounding these effects. Accumulating data suggests an important association between fructose intake, hyperuricaemia, hypertension, vascular disease, renal disease and the metabolic syndrome.[13] (See Figure 2.)

SESSION 3
RENAL TRANSPLANTATION

Professor S Powis and Dr P Harden

Professor Powis, Moorhead Professor of Renal Medicine, Royal Free & University College Medical School, London, discussed the effects of the increasing number of available immunosuppressive agents on three main areas of renal transplantation: improving transplantation outcomes, individualising therapy to reduce side-effects, and transplanting previously 'untransplantable' patients.

Review of trials of tacrolimus,[14] mycophenolate mofetil,[15] sirolimus[16] and basiliximab[17] demonstrate reduced acute rejection rates but no improvement in either graft or patient survival. Although the serum creatinine at one year predicts five-year graft survival,[18] there are no long-term prospective studies to predict graft survival. Despite the possibility of individualising immunosuppressive therapy to reduce side-effects, most centres use protocols based upon patient groups as a means to stratify immunosuppressive regimens in order to minimise steroid and/or calcineurin inhibitor exposure, e.g. accounting for the degree of HLA-matching, the presence of delayed graft function and acute rejection. It is encouraging that trials have indicated the feasibility of early calcineurin inhibitor withdrawal[19] as well as, separately, early steroid withdrawal[20] and avoidance.[21] Modern potent immunosuppressive agents facilitate transplantation in immunologically challenging circumstances. For example, the anti-CD20 monoclonal antibody rituximab has enabled transplantation across ABO blood groups and into positive crossmatch recipients.

Dr Harden, Consultant Nephrologist, Oxford Kidney Unit, Churchill Hospital, Oxford, reviewed the long-term outcomes of transplantation. Transplantation is an integral part of renal replacement therapy options, and improves life expectancy. However, various factors such as CAN, cardiovascular disease and malignancy impact on long-term outcomes.

There is evidence that the changes of CAN may develop as early as three months post transplantation,[22] possibly related to immune and inflammatory factors including donor disease and ischaemic injury, whilst the later development of CAN may involve calcineurin inhibitor toxicity. Early avoidance of calcineurin inhibitors is

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Electrolyte	Excretion assessment	Calculation	Normal Range
Sodium	Fractional Excretion (FE)	FE(Na) = (U[Na]/P[Na] x P[Creat]/U[Creat]) x 100%	FE(Na) = 1–3%
Potassium	Transtubular potassium gradient	U[K]/P[K] x P(Osm)/U(Osm)	TTKG = 6–8
Magnesium	Fractional Excretion	FE(Mg) = (U[Mg]/0·7P[Mg] x P[Creat]/U[Creat]) x 100%	FE(Mg) = <1%
Calcium	Urinary Calcium:Creatinine ratio	sing mmol/l for each	Ratio = 0·3–0·5
Chloride	Urinary Chloride	-	<20 mmol/l if depleted state
Hydrogen	Urinary pH Urinary anion gap (UAG)	U[Na]+U[K]-U[Cl]	UAG – Negative

TABLE 1 Electrolyte excretion dynamics.

possible by utilising mycophenolate mofetil[23] or sirolimus.[19] It is important to remember that there may be issues of 'under-immunosuppression' as a result of non-adherence. This may be critical in adolescents and young adults.

Cardiovascular disease is a significant cause of death in transplant recipients. Cardiovascular risk factors are similar to the general population, but also include graft dysfunction. There are few interventional studies in this area, but reduced cardiac death has been shown with lipid reduction in the ALERT study.[24] Malignancy is the second leading cause of death, and immunosuppressive agents may have variable effects on tumourigenesis,[25] although further studies are required.

SESSION 4
MANAGEMENT DILEMMAS

Dr L Plant and Dr R Greenwood

Dr Plant, Consultant Renal Physician, Cork University Hospital, Ireland, expounded the virtues of a systematic approach to electrolyte disturbances. He stressed the importance of evaluating the six main electrolytes (sodium, potassium, magnesium, calcium, chloride and hydrogen) in a systematic manner. He suggested that this should be performed by examining three areas:

1 'Total body' content – through history and examination findings e.g. blood pressure and extracellular fluid status in the case of sodium.
2 Serum concentration – through laboratory results in combination with e.g. ECG in the case of potassium and magnesium.
3 Excretion dynamics (see Table 1).

He illustrated the disturbances in Gitelman's syndrome, clearly explaining the pathophysiology through a dysfunction of the distal collecting tubule sodium chloride channel. The rationale underlying medical treatment with high dose amiloride (e.g. 20 mg) to block the epithelial sodium channel as well as electrolyte supplementation was explained. A second case study illustrated distal renal tubular acidosis. Dr Plant stressed the importance of oral bicarbonate supplementation (1 mmol/kg) to correct the acidosis and also to reduce the associated hypercalciuria. The latter should be assessed through regular measurement of the urinary calcium:creatinine ratio.

Dr Greenwood, Clinical Director, Renal Unit, Lister Hospital, Stevenage, ended the symposium with a holistic approach to patient care and tackled the difficult issue of conservative therapy for ESRD. Although dialysis is a life-saving procedure, it can be a harrowing and possibly futile experience for very frail and dependent individuals. Work performed at the Lister Hospital has shown the importance of measures of dependence such as the Karnofsky Score as predictors of survival. Furthermore, haemodialysis does not influence survival in high risk individuals who tend to be older with more co-morbidity and dependence.[26] The important role of a renal liaison team as the primary point of contact for the patient and family was highlighted. The importance of such a holistic approach to ESRD has been recognised within the Renal National Service Framework which has highlighted the importance of end-of-life individualised palliative care plans.

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PAST PRESIDENTS

Professor William Beilby (1783–1849)

In the days of Beilby and the famous Simpsons, Sir James Young Simpson and his equally distinguished nephew Sir Alexander Russell Simpson, midwifery was a specialty of medicine. The term 'Obstetrics' was not yet in use. In fact, the British College of Obstetrics and Gynaecology (known today as The Royal College of Obstetricians and Gynaecologists) was only founded by William Blair-Bell and Sir William Fletcher-Shaw in 1929.

Little is known about Beilby beyond the fact that he was born in Sheffield, and in 1807, apparently with no intention of becoming a doctor, went into the linen trade in Dublin. However, six years later, he entered the medical school in Edinburgh, qualifying after three years. His MD was on an obstetric topic and that remained his special interest for the rest of his professional life. In fact, his official title was 'Physician Accoucheur to the New Town Dispensary'.

President of the College from 1844–46, almost the only paper extant from that time is a letter to him from Sir James Young Simpson about an unseemly row he had had in a patient's house with the surgeon Mr Syme, offering an explanation and apologies. (It will be recalled that Simpson was himself to become President, from 1850–52.) On a happier note it was during Beilby's Presidency that the Great Hall of the College was built and officially opened, the President's address drawing heavily on Sibbald's autobiography.

Beilby was a devoutly evangelical Christian, deeply involved with what was then known as the Evangelical Alliance as well as being First President of a Medical Missionary Society, one of several springing up at that time of missionary outreach, particularly to the Indian subcontinent and Africa.

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