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SZAKORVOSI TOVÁBBKÉPZÉS

TÉMA: CLINICAL NEPHROLOGY

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C O N T E N T S

Part One

SECTIONS

TITLE OF PUBLICATIONS – AUTHORS – PUBLICATIONS

Part One

I. EPIDEMIOLOGY

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Alebiosu CO, Ayodele OE
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4. Hygiene hypothesis and prevalence of glomerulonephritis
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VI. TRANSPLANTATION

1. Co-infection of polyomavirus-BK and cytomegalovirus in renal transplant recipients
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3. Chronic organizing microangiopathy in a renal transplant recipient
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4. Recurrent glomerulonephritis in the renal allograft: an update of selected areas
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5. New insights into the pathogenesis and the therapy of recurrent focal glomerulosclerosis
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6. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience
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8. Impact of statin treatment on 1-year functional and histologic renal allograft outcome
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9. Effect of sirolimus on mesangial cell cholesterol homeostasis: a novel mechanism for its action against lipid-mediated injury in renal allografts
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C O N T E N T S

1. The global burden of chronic kidney disease and the way forward

Alebiosu CO, Ayodele OE

Ethn Dis 2005 15 (3): 418-23.

Background: Chronic kidney disease (CKD) is increasing worldwide at an annual growth rate of 8%. Regional differences exist in the epidemiology of the condition, and non-Whites are more affected. Methods: An English-language literature search using Medline (January 1984-October 2003) was done to assess research/review articles on burden and prevention of CKD. Particular attention was paid to epidemiology and prevention of chronic kidney diseases. Results: The prevalence of CKD is higher in developing countries than in the developed world. The most common causes of CKD in the developing countries are chronic glomerulonephritis and systemic hypertension, diabetic nephropathy being the most common cause in Europe, the United States, and Japan. Factors contributing to the regional differences in the etiology and prevalence of CKD are race and ethnicity, genetic predisposition, increasing prevalence of type 2 diabetes, mortality caused by other disease obesity, and possibly cigarette smoking. The control of hypertension, dyslipidemia, proteinuria, obesitiy, avoidance of low birth weight, smoking, and preventing ingesting of heavy metals such as lead are intervention strategies that retard or prevent progression of renal diseases. The magnitude of the existing burden of illness caused by renal failure, the projection for increasing incidence of CKD, and the limitations of our existing treatments for renal insufficiency all point to the need for clinical and population-based interventions aimed at prevention of CKD. Conclusions: A comprehensive health education campaign and screening of the general populace are needed in order to detect chronic kidney disease early. These measures will ensure appropriate and timely institution of proven mesures to halt or reduce progression of CKD.

2. Demographics and presenting clinical features of childhood systemic lupus erythematosus

Faller G, Thomson PD, Kala UK et al.

S Afr Med J 2005 95 (6): 424-7.

Objectives: To review the presentation and characteristics of children with systemic lupus erythematosus (SLE). Methods: The records of children with sufficient American College of Rheumatology (ACR) criteria for SLE treated by the renal units of the Johannesburg and Chris hani Baragwanath hospitals, and the artritis clinic of the Johannesburg Hospital between january 1974 and March 200 were revied. The clinical presentation, age distribution and race were examined. Results: A total of 36 children met the criteria. There were 26 girls and 10 boys, with a mean age of 11,5 and 10,2 years respectively. The male-to-female ratio was 1:2,6 overall, with ratio of 1:1,2 under 10 years and 1:4 over 10 years. There were 15 white, 2 Indian and 5 coloured patients. The 14 black patients all presented after 1986. Rashes were found to be the commonest clinical features present at the time of diagnosis, followed by polyarthritis and renal pathology. Constitutional symptoms were common, as were generalised lymphadenopathy and hepatosplenomegaly, while neurological, pulmonary and cardiac sings and symptoms were less common. Renal disease was present in 58% of patients on presentation. Conclusion: There is a diverse array of presenting features in childhood SLE. There has been increased recognition of the disease in young black South Africans since 1986.

3. Different regional dynamics of end-stage renal disease in Japan by different causes

Kato N, Usami T, Fukuda M, et al.

Nephrology (Carlton) 2005 10 (4): 400-4.

Summary Background: We recently showed that there were clear regional differences in the dynamics of end-stage renal disease (ESRD) within Japan, which has an ethnically homogenous population. We speculate on the reason for these regional differences by correlating the regional distributions in the incidence of ESRD due to each of the following individual causes of ESRD: chronic glomerulonephritis (CGN), diabetic nephropathy (DMN) and polycystic kidney disease (PKD). Methods: The number of ESRD patients entering maintenance dialysis therapy due to individual causes of renal disease in each prefecture was reported annualy for a 6-year period by the Japanese Society for Dialysis Therapy. After combining data from several prefectures into 11 geopolitical regions in Japan, the mean annual incidence of ESRD across the 11 regions was correlated among the three causes of ESRD. Results: There were significant regional differences in the incidence of ESRD due to CGN ($P < 0,0001$) and DMN ($P = 0,0015$), the distributions of which were similar to each other across the 11 regions. In contrast, no regional differences were found in the incidence of ESRD due to PKD ($P = 0,6$) as the major genetic disorder of the kidneys, suggesting that genetic background are relatively uniform throghout Japan. The regional distributions due to PKD were not correlated with those due to other causes: CGN and DMN. Conclusion: Risk factors common to nephropathy progression, rather than an underlying disease incidence and genetic predisposition, might contribute to regional differences in the overall ESRD incidence in Japan. Other possibilities such as the prevalence of underlying diseases, and acceptance or rejection rates into treatment programmes must be considered further for better explanations.

4. Hygiene hypothesis and prevalence of glomerulonephritis

Hurtado A, Johnson RJ

Kidney Int Suppl 2005 97: S62-7.

The hygiene hypothesis was proposed to explain the marked increase in allergies that has been observed in industrialized (Westernized) societies. This hypothesis proposes that early and frequent exposure to bacterial and other antigens, such as is common in developing nations, leads to a normal Th1 response, but that better public hygiene and less infections observed in industrialized nations may lead to persistence of the Th2 phenotype and thereby increase our risk for developing allergies. Infection early in life with measles or hepatitis A virus, immunization with bacille Calmette-Guerin, certain gastrointestinal bacteria (lactobacillus), and environmental endotoxin exposure may protect individuals from developing allergy in adulthood. Paradoxically, infestation by parasites stimulates a Th2-cell response; however, the incidence of allergic disease is very low, perhaps due to the stimulation of T-regulatory lymphocytes that can downregulate Th1 and Th2 responses. Some types of human glomerulonephritis (GN) have Th1-predominant immune response, including crescentic and membranoproliferative GN, whereas other types of GN have a predominant Th2 immune response, including membranous nephropathy, minimal change disease, and immunoglobulin A nephropathy. A review of the prevalence of specific GN shows that the higher prevalence of membranoproliferative GN in developing countries and the higher frequency of immunoglobulin A nephropathy and minimal change disease in industrialized countries could be explained by the hygiene hypothesis. We suggest that studies examining Th1/Th2 balance, particularly as it develops in childhood, should be performed to determine of early polarization of the immune response is responsible for the later development of specific forms of GN.

5. Alport syndrome in southern Sweden

Persson U, Hertz JM, Wieslander J, et al.

Clin Nephrol 2005 64 (2): 85-90.

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Abstract Aim: The aim of the present investigation is to study the epidemiology of Alport syndrome in southern Sweden, to search for mutations in the COL4A5 gene and to estimate the mutation frquency. Patients and methods: Patients with suspected Alport syndrome were identified in an area with a population of 1,45 million. Clincal criteria were used to estabilish

the diagnosis and samples for mutation analysis were collected. Mutation analyses were performed with Single-Stranded Conformation Polymorphism analysis (SSCP) of PCR-amplified genomic DNA. Results: Altogether 25 families with hereditary nephritis were identified. Alport syndrome with X-linked transmission was evident in 14 families, with juvenile (< 31 years) progression to end-stage renal failure (ESRF) in ten and adult (≥ 31 years) in four families. Conclusion: The frequency of males with X-linked disease was calculated to one in 17,000 male births (95% confidence interval (CI) 1/10,500 - 1/28,600), and the prevalence to one in 40,000. A total of seven females with ESRF were identified, with a median age at ESRF of 45 years. The male to female ratio of cases with ESRF was 4,9 to 1. The risk of developing ESRF among females was from the expected incidence roughly estimated to 12%. Patients with X-linked disease constituted 1,8% of patients with ESRF in the examined area. A mutation was identified positive in 10 of 14 families with X-linked disease, but never in families not fulfilling the clinical criteria for Alport syndrome. In families with juvenile phenotype and positive mutation analysis, the mutation frequency was calculated to between 1/78,00 and 1/198,000 (95%, CI 1/42,000 - 1/177,000) if the effective fertility was estimated to be between 0 and 0,2.

6. Clinicopathological and epidemiological analysis of amyloidosis in Turkish patients

Ensari C, Ensari A, Tümer N, et al.

Nephrol Dial Transplant 2005 20: 1721-5.

Abstract Background: The aim of the present was assess the correlation of immunohistochemical subtyping with clinical diagnosis in order to achieve useful epidemiological data regarding amyloidosis in Turkish patients. Methods: We carried out immunohistochemical studies on 128 biopsies from various sites of 111 patients with biopsy-proven amyloidosis and, based on the results, classified the patients. We assessed the correlation of immunohistochemical subtype with clinical diagnosis and gathered epidemiological data. Results: The sites most biopsied were kidney and rectum, followed by the testicle, liver, small intestine and bladder. Amyloid deposits showed positive staining with a single antibody in 120 biopsies. Pure amyloid A (AA) positivity was seen in 113 biopsies: six biopsies were positive for amyloid lambda (AL) and one for ß2-microglobulin (ß2MG). The clinical diagnoses of 81 patients (98 biopsies all AA positive) were suggestive of familial Mediterranean fever (FMF). Also AA positive were eight patients with tuberculosis, seven patient with rheumatoid arthritis, four patients with bronchiectasis and one patient with Crohn's disease. The biopsies from seven patients clinically suspected to have plasma cell dyscrasias were AL positive. One patient undergoing haemodialysis was ß2MG positive. Two patients without definite diagnoses showed double or triple positivity, which could not be interpreted and classified immunohistochemically. Conclusion: This study demonstrates that the predominant association of AA amyloidosis is with FMF. It also suggest that the routine immunohistochemical study of patients with amyloidosis who are of certain ethnic backgrounds suffices for classifying the subtype of amyloid fibril protein and related disease.

7. Prevalence of chronic renal failure in adults in Delhi, India

Agarwal SK, Dash SC, Irshad M, et al.

Nephrol Dial Transplant 2005 20: 1638-42.

Abstract Background: Chronic renal failure (CRF) is a debilitating condition responsible for high morbidity and mortality and is a financial burden on goverment and society. Because of its costs and the complexity of its treatment, proper care is available to very few patients in India. A community-based study has not been done to determine the prevalence of CRF in India. Methods: We used a multi-stage cluster sampling method in the South Zones of Delhi. In each area, we first contacted the local social leader and explained the study and the medical information pamphlets. On pre-scheduled days, the study team canvassed the study zone. The individuals contacted responded toa detailed questionnaire, and had a physical examination, a dipstick urine test for albumin and sugar and a blood test for serum creatinine. A serum

creatinine >1,8 mg% defined renal failure. A repeat test for serum creatinine was done after 8-12 weeks to confirm chronicity of renal failure. If it was >1,8mg% after 3 months in absence of reversible factors, CRF was diagnosed. The person found to have CRF was asked to attend a hospital renal clinic for futher investigations and individualized management. Results: A total of 4972 persons were contacted for the study. Their mean age was 42±13 years; 56% were males. Out of the 4972 who were initially approached, 4712 agreed to give the blood sample, and thus were included for the evaluation of CRF. CRF was found in 37 of them. Thus, the prevalence of CRF in that adult population was 0,785% or 7852/million. Conclusion: The prevalence of CRF in India makes it a serious problem in need of urgent efforts to contain it.

II. ETIOLOGY

1. Glomerulonephritis associated with acute pneumococcal pneumonia: a case report

Phillips J, Palmer A, Baliga R.

Pediatr Nephrol 2005 Jul 12 [Epub ahead of print]

Abstract Streptococcus pyogenes is the most common cause of post-infectious glomerulonephritis. There have been isolated case reports of nephritis following infections with Streptococcus pneumoniae. We report here the case of a 6-year-old white female who presented with blood culture-confirmed pneumococcal pneumoniae associated with glomerulonephritis. Her acute renal failure improved over several days, and renal function was normal by 8 weeks post-hospitalization. This case serves to reinforce the concept that other organisms besides Streptococcus pyogenes can trigger a similar post-infectious glomerulonephritis and should be considered in the differential diagnosis of any child who presents with acute glomerulonephritis and respiratory findings. Additionally, pneumococcus group 7 may be a nephritogenic strain and requires further investigation.

2. Molecular technique identifies the pathogen responsible for culture negative infective endocarditis

Shin GY, Manuel RJ, Chori S et al.

Heart 2005 91 (6): e47.

Abstract A case of culture negative endocarditis complicated by immune comple glomerulonephritis and severe aortic regurgitation necessitated aortic valve replacement. Empirical treatment with penicillin and gentamycin according to UK guidelines was started. The pathogen, Streptococcus sanguis, was later identified by polymerase chain reaction (PCR) amplification and sequencing of bacterial 16S ribosomal RNA. This molecular technique is likely to be of increasing importance in determining the aetiology of culture negative infective endocarditis, thus providing essential treatment and epidemiological information.

3. Hepatitis C virus RNA and core protein in kidney glomerular and tubular structures isolated with laser capture microdissection

Sansonno D, Lauletta G, Montrone M et al.

Clin Exp Immunol 2005 140 (3): 498-506.

Abstract The role of hepatitis C virus (HCV) in the production of renal injury has been extensively investigated, though with conflicting results. Laser capture microdissection (LCM) was performed to isolate and collect glomeruli and tubules from 20 consecutive chronically HCV-infected patients, namely 6 with membranoproliferative glomerulonephritis, 4 with membranous glomerulonephritis, 7 with focal segmental glomerulosclerosis and 3 with IgA-nephropathy. RNA for amplification of specific viral sequences was provided by terminal continuation methodology and compared with the expression profile of HCV core protein. For each case two glomeruli and two tubular structures were microdissected and processed. HCV RN sequences were demonstrated in 26 (65%) of 40 glomeruli, but in only 4 (10%) of the tubules ($P < 0,05$). HCV core protein was concomittant with viral sequences in the glomeruli and present in 31 of 40 tubules. HCV RNA and/or HCV core protein was found in all four disease types. The immunohistochemical picture of HCV core protein was compared with the LCM-based immunoassays of the adjacent tissue sections. Immune deposits were detected in 7 (44%) of 16 biopsy samples shown to be positive by extraction methods. The present study

indicates that LCM is a reliable method for measuring both HCV RNA genomic sequences and HCV RNA genomic sequences and HCV core protein in kidney functional structures from chronically HCV-infected patients with different glomerulopathies and provides a useful baseline estimate to define the role of HCV in the production of renal injury. The different distribution of HCV RNA and HCV-related protein may reflect a peculiar 'affinity' of kidney microenvironments for HCV and point to distinct pathways of HCV-related damage in glomeruli and tubules.

4. Hepatitis B virus genotypes and extrahepatic manifestations

Cacoub P, Saadoun D, Bourliere M et al.

J Hepatol 2005 Aug 5 [Epub ahead of print]

Abstract Backgroun/Aims: This study aimed at correlating the presence of extrahepatic manifestations with hepatitis B virus (HBV) genotypes in patients with chronic HBV infection. Methods: This was a national (France), multicenter, retrospective, cross-sectional study. HBV genotypes were determined in 190 patients HbsAg-positive for at least 6 months and documented before any treatment. Results: Patients were aged 42 +/- 15 years and mainly male (77%). Alcohol intake was high in 6% of them, ALT elevated in 73%; 27% were cirrhotic. All HBV genotypes were found, mainly A (24%), D (29%), C (11%), and E (10%). Thirty (16%) patients had clinical extrahepatic manifestations, mainly sensory-motor deficiency, sicca syndrome, myalgia, glomerulonephritis, and arthralgia-arthritis. Their presence was not related to any epidemiologic, viral (including genotypes) or hepatic factor, but to a higher platelet count (P=0,004). Twenty-nine (15%) patients had biological extrahepatic manifestations, mainly anti-smooth muscle, antinuclear, and anti-nucleosome antibodies. Their presence was related only to anti-Hbe antibodies positivity (P=0,007) or elevated platelet count (P=0,003). Carrying precore mutant HBV increased by 2,8 folds the risk to have at least one extrahepatic biological manifestation. Conclusion: No relationships between HBV genotypes and the presence of extrahepatic manifestations were evidenced in patients with chronic HBV infection.

5. Polyarteritis nodosa revisited

Colmegna I, Maldonado-Cocco JA

Curr Rheumatol Rep 2005 7 (4): 288-96.

Abstract Polyarteritis nodosa (PAN), the prototype of systemic vasculitis, is a rare condition characterized by necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Sing and symptoms of this disease are primarily attributable to diffuse vascular inflammation and ischemia of affected organs. Virtually any organ with the exception of the lungs may be affected, with peripheral neuropathy and symptoms from osteoarticular, renal artery, and gastrointestinal tract involvement being the most frequent clinical manifestations. A clear distinction between limited versus systemic disease and idiopathic versus hepatitis B related PAN should be done because there are differences in the implicated pathogenetic mechanisms, their treatment, and prognosis. Currently, corticosteroids plus cyclphosphamide is the standard of care for idiopathic PAN, in particular for patients with adverse prognostic factors (more severe disease), in whom this combination prolonged survival. In contrast for hepatitis B related PAN treatment consists of schemes that include plasmapheresis and antiviral agents.

6. Familial Mediterranean fever and mesangial proliferative glomerulonephritis: report a case and review of the literature

Cagdas DN, Gucer S, Kale G et al.

Pediatr Nephrol 2005 20 (9): 1352-4.

Abstract In familial Mediterranean fever (FMF), a genetically inherited disease characterized by fever and serositis, renal involvement is mainly AA amyloidosis. We report a patient with FMF who developed mesangial proliferative glomerulonephritis; presumably in response to colchicine treatment, the activity of the disease decreased and renal function tests and urinary findings normalized. This report emphasizes the concurrent existence of mesangial proliferative glomerulonephritis with FMF in the absence of renal amyloidosis. Due to increased inflammatory response observed in FMF, immunologic glomerular injury, a common cause of glomerulonephritis, may occur more frequently in patients with FMF.

7. Rapidly-progressive glomerulonephritis complicating Behcet's disease: successful treatment with intravenous cyclophosphamide

Kim SD, Kim SH, Kim HR et al.

Rheumatol Int 2005 Jun 29 [Epub ahead of print]

Abstract We report a case of rapidly-proliferative glomerulonephritis complicating Behcet's disease (BD). A 44-year-old male has suffered from recurrent oral ulcers and retinal vasculitis developed 2 years ago. He complained of abdominal pain and papulopustular skin lesions. Multiple ulcers were seen on the colon on colonoscopy. Routine renal work-up revealed heavy proteinuria and hematuria. Renal biopsy demonstrated crescentic glomerulonephritis. Most symptoms improved after steroid therapy, except for urinary abnormalities. At this point, intravenous monthly cyclophosphamide pulse therapy was undergone. After the sixth pulse therapy, proteinuria and hematuria were dramatically improved and renal function was well preserved.

8. Amyloidosis associated with chronic lymphocytic leukemia

Ikee R, Kobayashi S, Hemmi N et al.

Amyloid 2005 12 (2): 131-4.

Abstract Chronic lymphocytic leukemia (CCL), the most common form of leukemia in Western countries, rarely induces glomerular disease, but membranoproliferative glomerulonephritis or immunotactoid glomerulopathy has been reported. The proliferating cells in CCL are of mature B-cell origin and produce monoclonal immunoglobulin (Ig), thus leading to various kinds of autoimmune disorders or immunotactoid glomerulopathy. Although there have been a few reported cases of amyloid accompanying CLL, the type of amyloid fibrills has not been demonstrated nor described in detail, particularly regarding monoclonal Ig productivity. We report a rare case of amyloidosis associated associated with CLL, in which we detected light chain type monoclonal Ig in the sera, urine, and on the surface membrane of lymphocytes, and discuss an association between monoclonal Ig-related disease and non-Hodgkin's lymphoma.

9. Sarcoid granulomatous interstitial nephritis and sarcoid abdominal aortic aneurysms

Hatta T, Tanda S, Kusaba T et al.

Nephrol Dial Transplant 2005 20: 1480-2.

Abstract Sarcoidosis is a systemic granulomatous disorder of umknown etiology, characterized by chronic non-caseating epitheloid granulomatous inflammation with tissue destruction. Renal involvement affects ~20% of patients with sarcoidosis and can be found in patients with no other localizations of the disease. A common cause of renal dysfunction is hypercalcaemia and hypercalcuria leading to nephrocalcinosis. Granulomatous interstitial nephritis (GIN) is also a cause of renal dysfunction, in which the clinical picture and laboratory evidence of tubular defects points to tubulo-interstitial nephritis. Sarcoidosis is a systemic disease, affecting many organs. However, large vessel involvement such as aortic aneurysms due to sarcoidosis are rare, and only a few papers have reported aortic aneurysms

complicating sarcoidosis. We report a case of renal sarcoidosis complicated with saccular abdominal aortic aneurysms, confirmed by histology of the surgically resected aortic wall. Conclusion We report on a patient with renal sarcoidosis found by renal biopsy and complicated with abdominal aortic aneurysms that were discovered by chance. Aneurysm surgery was performed and renal dysfunction was improved by corticosteroid therapy. Aortic aneurisms along with renal involvement in sarcoidosis form an exceptional morbid association with a hihg inherent risk of death by aneurysm rupture if corticosteroid therapy is started before vascular surgery. We therefore suggest that aortic imagimg, at least by ultrasonography, should be performed in the case of systemic sarcoidosis.

10. Different glomerulopathies accompanying non-smalll-cell lung cancer

Paydas S, Soydas B, Paydas S et al.

Mt Sinai J Med 2005 72 (4): 279-81.

Abstract The coexistence of lung cancer and glomerular lesion is not commonly reported. Malignancy-related glomerulopathy is commonly membranous glomerulonephritis. Other glomerulopathies are seldom reported. We report two cases presenting with non-small-cell, acute renal failure and nephrotic syndrome secondary to membranoproliferative glomerulonephritis and amyloidosis.

11. Peritubular capillary injury in Chinese herb guan-mu-tong - induced acute tubular necrosis

Yang L, Li XM, Wang SX et al.

Zhonghua Nei Ke Za Zhi 2005 44 (7): 525-9.

Objective: To explore the role and mechanisms of peritubular capillary (PTC) injury in the progression of Chinese herb guan-mu-tong (GMT), aristolochiae mansuriensis kom) induced acute tubular necrosis (GMT-ATN). Methods: Renal biopsy tissues from 4 cases of GMT-ATN and 5 cases of antibiotic induced ATN (A-ATN) were included in the study. Tubulointerstitial injury was sem-quantitatively assessed. Immunohistochemical SP method was applied to reveal PTC as well as the expression of vascular endothelial growth factor (VEGF). Ultra microstructure of endothelial cells and basement membrane of PTC was detected by electronic microscopy (EM). 5 cases of minor mesangioproliferative non-IgA glomerulonephritis were selected as a control group. Results: The density of PTC was decreased significantly in GMT-ATN, as compared with the A-ATN and control group (211.08 +/- 56,15 vs 413.54 +/- 66.59, 536.62 +/- 68.38, P < 0,01). Dilated and deformed PTC lumina were noted in GMT-ATN with some endothelial cells and basement membrane partially disrupted. Most endothelial cells were found to be swollen with vacuoles dispersed in the cell plasma. The basement membrane was partially shrunk and thickened. The expression of VEGF in renal tubular epithelial cells (RTEC) was much less in the GMT-ATN than in A-ATN group 2.1 (0 approximately 3.86)% vs [42.5 (31.33 approximately 60.25)%, P < 0,01], even though it was higher than that in the control group [23.1 (18.2 approximately 39.5)%, P < 0,01]; the expression was correlated with PTC density. Close cerrelation was also found between RTEC regeneration and PTC density, as well as VEGF expression (r = 0.880 and 0.802 respectively, P < 0,01). Conclusions: PTC was markedly injured in GMT-ATN; this could be one of the cause for the continously progressing tubulointerstitial damage. The low expression of VEGF in RTEC might contribute to the PTC injury process.

III. PATHOGENESIS

1. Hygiene hypothesis and prevalence of glomerulonephritis

Hurtado A, Johnson RJ

Summary: See Part 2/EP/4

2. Apoptosis in glomerulonephritis

Hughes J, Savill JS

Curr Opin Nephrol Hypertens 2005 14 (4): 389-95.

Abstract Purpose of Review: Although glomerular cell apoptosis may be detrimental in acute and chronic inflammation, it is also key component of reparative glomerular remodelling that can follow injury. All glomerular cells are vulnerable to apoptosis although there are often differences in the nature of the initiating stimulus and the factors that are protective. The purpose of this review is to outline how modulation of this process may inhibit glomerular injury and promote tissue repair. Recent Findings: In vitro studies are providing more information on the factors that regulate apoptosis in individual glomerular cell types. It has now become apparent that growth factors such as vascular endothelial growth factor may have protective actions on several cell types and this facilitate future treatments that promote the survival of multiple cell types within injured glomeruli. Work in this field has also emphasized that many current treatment strategies may exert a beneficial impact upon renal cell death. Summary: Although the advent of various antiapoptotic agents such as caspase inhibitors and recombinant growth factors does provide future opportunities to modulate apoptosis for therapeutic gain in patients with glomerulonephritis, there is still some way to go before such reagents are used to treat human disease. However, there is scope for optimism that such treatment will reach the clinic in due course.

3. Apoptosis and proliferation in childhood acute proliferative glomerulonephritis

Ozaltin F, Besbas N, Bakkaloglu A et al.

Pediatr Nephrol 2005 Jun 18 [Epub ahead of print]

Abstract Acute proliferative glomerulonephritis is characterized by glomerular hypercellularity that can be caused by many different etiologies and pathogenic mechanisms. A balance between cell birth by mitosis and cell death by apoptosis is crucial. In this study, apoptosis and regenerative activity (Ki67/apoptosis index) were investigated in acute proliferative glomerulonephritis. Thirty-five children with biopsy-proven acute proliferative glomerulonephritis and five controls with MCD studied retrospectively. According to the clinical outcome, patients were divided into 2 groups: group 1 (n=21) were patients with normal renal functions at follow-up; group 2 (n=8) were patients with end-stage renal failure or those died. Immunohistochemical staining of proliferating cells (Ki67) was done. In situ end labeling of DNA was used to evaluate apoptosis. Glomerular cell apoptosis was 48% in the patients with acute proliferative glomerulonephritis and 3% in controls ($p < 0,001$). Apoptotic cells were identified in the tubulointerstitial copartment with higher and heavier immunostaninig in patients than controls ($p = 0,001$). Tubular proliferative index (= tubular proliferation/tubular apoptosis ratio) was significantly higher in group 1 patients than in group 2 patients (2,03 +/- 2% versus 0,32 +/- 0,6%, $p = 0,002$). Tubulointerstitial regenerative ratio (tubular proliferation/interstitial proliferation ratio) was significantly higher in controls than in patients ((3,4 +/- 1,9 versus 1,52 +/- 0,8, $p = 0,01$). In addition, it was significantly increased in group 1 patients when compared with those in group 2 patients (1,89 +/- 0,8 versus 0,73 +/- 0,2, $p = 0,001$). Since 17 patients presented with postinfectious proliferative

glomerulonephritis, which is known to exhibit better course, we also evaluated those parameters in patients with postinfectious proliferative glomerulonephritis separately. We found statistically significant differences only in the tubulointerstitial regenerative ratio, which was higher in postinfectious cases when compared with those in other cases [1,60 interquartile range (IQR) 1,54 versus 1,22 IQR 1,26, respectively, p = 0,003]. Conclusion: The tubular proliferative index and tubulointerstitial regenerative ratio might be useful parameters for predicting final functional outcome in acute proliferative glomerulonephritis. Further studies, however, are still needed to clarify the importance of these histopathological parameters.

4. Synergistic effect of hypoxia and TNF-alpha on production of PAI-1 in human proximal renal tubular cells

Li X, Kimura H, Hirota K et al.

Kidney Int 2005 68 (2): 569-83.

Abstract Background: Chronic hypoxia has been newly proposed as a common mechanism of tubulointerstitial fibrosis in the progression of various chronic inflammatory renal diseases, where plasminogen activator inhibitor-1 (PAI-1) plays an inportant role in the accumulation of extracellular matrix (ECM) through inhibition of plasmin-dependent ECM degradation. In the present study, we investigated the presence of PAI-1 in renal tubular cells by immunostaining renal biopsy samples. We also closely examined the effects of hypoxia and tumor necrosis factor-alpha (TNF-alpha) on PAI-1 expression in cultured human proximal renal tubular cells (HPTECs). Methods: Confluent cells growth-arrested in Dulbecco's modified Eagle's medium (DMEM) for 24 hours were exposed to hypoxia (1% O(2)) and/or TNF-alpha at 10 ng/ml for up to 48 hours. Amounts of PAI-1 protein and mRNA after stimulation were measured by enzyme-linked immunosorbent assay (ELISA) and TaqMan quantitative polymerase chain reaction (PCR) or cDNA array analysis, respectively, and compared to those in cells incubated under control conditions (18% O(2) without TNF-alpha). Hypoxia-inducible factor-alpha (HIF-1alpha) was demonstrated by immunoblot and immunofluorescence analyses. Human PAI-1 promoter activity was estimated by luciferase reporter gene assay. Results: In crescentic glomerulonephritis, clusters of proximal tubules were specifically stained for PAI-1. cDNA array analysis identified PAI-1 as a major gene highly induced by hypoxia in HPTECs. Treatment of 24 hours with hypoxia, TNF-alpha, and their combination induced a 2,8-fold, a 1,8-fold, and 4,6-fold increase in PAI-1 protein secretion, and produced a 3,6-fold, a 3,3-fold, and a 12,1-fold increase at the PAI-1 mRNA level, respectively. Immunoblot analysisand immunocytochemistry revealed that hypoxia-inducible factor-alpha (HIF-1alpha) was markedly accumulated in the cell lysates and exclusively translocated to nuclei after 16 hours'exposure of HPTECs to hypoxia but not to TNF-alpha. Luciferase reporter gene assay showed that hypoxia, TNF-alpha, and their combination increased PAI-1 transcription activity by 1,8-fold, 1,4-fold, and 2,2-fold, respectively. A dominat-negative form of HIF-1alpha significantly suppressed PAI-1 transcription activity induced by hypoxia. Inhibition of nuclear factor-kappaB (NF-kappaB) caused a moderate decrease in PAI-1 production under hypoxia. Conclusion: Hypoxia induces PAI-1 expression via remarkable nuclear accumulation of HIF-1alpha and partially via NF-kappaB activation in HPTECs. TNF-alpha can sinergistically enhance this hypoxia-induced PAI-1 expression.

5. Oxidative stress in children with kidney disease

Pavlova EL, Lilova MI, Savov VM

Pediatr Nephrol 2005 Jul 7 Fepub ahead of print]

Abstract The aim of this work was to study the dynamics of oxidative stress in the blood and urine of children with kidney disease: glomerulonephritis (GN), pyelonephritis (PN), renal failure (RF), and lower urinary tract infections (LUTI). The concentration of conjugated dienes is increased in blood: GN times and RF up to 2 times; and extremely increased in urine; GN 12 times and RF 4 times. The concentration of thiobarbituric acid reactive substances in urine shows a similar trend: GN 7 times, RF 1,5 times, and LUTI almost 3 times. Urine

chemiluminescence is also increased: GN 5 times, PN and LUTI 3 times, and RF 6 times. Kidney disease leads to 2,5-fold inhibition of antioxidant catalase activity in blood and 10-fold in urine. Total antioxidant activity of urine is induced in all groups: GN 18 times, PN 2 times, RF 1,5 times, and almost 4 times in the LUTI group. Experimental data confirm that produtcts of lipid peroxidation, intensity of chemilumunescence, and total and enzyme antioxidant capacity in combination with clinical parameters area proper test for the dynamics of oxidative stress and markers of intoxication in children with inflammatory and immunological active parenchymal kidney disorders. These data could be helpful for the opitimalization of complex and effective antioxidant therapy of children with kidney disease.

6. Mesangial cells and glomerular inflammation: from the pathogenesis to novel therapeutic approaches

Gomez-Guerrero C, Hernandez-Vargas P, Lopez-Franco O et al.

Curr Drug Target Inflamm Allergy 2005 4 (3): 341-51.

Abstract The mesangium occupies a central anatomical position in the glomerulus, and also play an important regulatory role in immune-mediated glomerular diseases, with an active participation in the response to local inflammation . In general, the mesangial cell responses to the pathological stimuli are associated with the main events of glomerular injury: leukocyte infiltration, cell proliferation and fibrosis. Leukocyte migration and infiltration into the glomerulus is reponsible for the initiation and amplification of glomerular injury, and is mediated by adhesion molecules and chemokines, which can be locally synthesized by mesangial cells. The increase in mesangial cell number is also due to proliferation of intrinsic mesangial cell population. Regulatory mechanisms of mesangial cell replication include a complex array of factors which control cell proliferation, survival and apoptosis. Mesangial matrix accumulation leading to glomerulosclerosis, is a consequence of an imbalance between matrix production and degradation, and is controlled by growth factors and pro-inflammatory cytokines. The initial phase of immune-mediated glomerular inflammation depends onthe interaction of immune complexes with specific Fc receptors in infiltrating leukocytes and resident mesangial cells, the ability of immune complexes to activate complement system, and on local inflammatory process. Activated mesangial cells then produce many inflammatory mediators leading to amplification of the injury. This review will focus on the biological function of mesangial cells that contribute to glomerular injury, with special attention to immune-mediated glomerulonephritis. Furthermore, new therapies based on the pathophysiology of the mesangial cell that being developed in experimental models are also proposed.

7. Hepatocyte growth factor and its receptor Met are induced in crescentic glomerulonephritis

Rampino T, Gregorini M, Camussi G et al.

Nephrol Dial Transplant 2005 20 (6): 1066-74.

Abstract Background: In experimental extracapillary glomerulonephritis (EG) podocytes migrate, proliferate and change phenotype, and play a pivotal role in crescent formation. Hepatocyte Growth Factor (HGF) is an injury.induced effector of tissue repair that causes cell migration, growth and transdifferentiation via its receptor Met. Methods: In 11 patients with EG we measured serum levels of HGF and investigated whether serum induces the release of HGF by Periferal Blood Mononuclear Cells (PBMC). In renal biopsies we studied the expression of Met. In cultured podocytes we studied Met expression, migration, growth and morphological changes induced by recombinant (r) HGF. Results: In patients with EG average serum levels of HGF (0,73 ng/ml) where higher than in normal volunteers (N, 0,10 ng/ml), p<0,01) and in patients with non-crescentic glomerular disesase (CD, 0,18 ng/ml, p<0,01). Serum of EG induced a significant HGF release by PBMC (mean 0,58 ng/ml) in comparison with serum of N and CD (0,07 and 0,06 ng/ml, respectively, both p<0,001). Met was strongly expressed in crescents. Cultured podocytes expressed Met, and rHGF induced in podocytes a time- and dose-dependent migration, growth and epithelial to mesenchymal

transdifferentiation. Conclusion: These resutls suggest that HGF/Met system participates in the process of crescent formation by inducing podocyte migration, growth and mesenchymal transformation.

8. Expanding the pathologic spectrum of light chain deposition disease: a rare variant with clinical follow-up of 7 years

Chang A, Peutz-Kootstra CJ, Richardson CA et al.

Mod Pathol 2005 18 (7): 998-1004.

Abstract We report an unusual histologic manifestation of light chain deposition disease in a 69-year-old female patients, who presented with nephrotic syndrome and an increased serum creatinine. The renal biopsy findings by light and electron microscopy suggested a glomerulonephritis with massive immune-complex deposition, such as lupus nephritis. However, the overall clinical scenario was inconsistent with lupus. Subsequent tests revealed multiple myeloma confirmed by bone marrow biopsy and identification of a monoclonal kappa light chain immunoglobulin by serum and urine immunoelectrophoresis and immunofixation. Additional immunohistochemistry of the first biopsy also demonstrated strong kappa light chain staining of the glomerular capillary walls and mesangium but not lambda light chain or IgG staining. The patient responded well to therapy and was asymptomatic until nearly 7 years later. A repeat biopsy revealed similar findings to the first biopsy with the addition of immunofluorescence microscopy, which confirmed the prominent kappa light chain staining of the glomeruli, tubular basement membranes, and interstitium with corresponding electron-dense deposits visualized by electron microscopy. This case represents an unusual histologic variant of light chain deposition disease, which to our knowledge has not been previously described and further expands the wide cinicopathological spectrum within the diagnostic entity of light chain deposition disease.

9. Clinicopathological and epidemiological analysis of amyloidosis in Turkish patients

Ensari C, Ensari A, Tümer N et al.

Nephrol Dial Transplant 2005 20: 1721-5.

Summary: See Part 2/EP/6

10. Amyloidosis associated with chronic lympocytic leukemia

Ikee R, Kobayashi S, Hemmi N et al.

Amyloid 205 12 (2): 131-4.

Summary: See Part 2/ET/8

11. Hepatitis C virus RNA and core protein in kidney glomerular and tubular structures isolated with laser capture microdissection

Sansonno D, Lauletta G, Montrone M et al.

Clin Exp Immunol 2005 140 (3): 498-506.

Summary: See Part 2/ET/3

12. Low fetuin-A levels are associated with cardiovascular death: Impact of variations in the gene encoding fetuin

Stenvinkel P, Wang K, Qureshi AR et al.

Kidney Int 2005 67 (6): 2383-92.

Abstract Background: Vascular calcification is a common among end-stage renal disease (ESRD) patients and a central characteristic of the atherosclerotic cardiovascular disease observed in dialysis patients. Fetuin-A, a circulating calcium-regulatory glycoprotein that inhibits vascular calcification, is associated with inflammation and outcome in dialysis patients. In the present study, we evaluated the association between fetuin-A, clinical phenotype, and outcome, as well as the impact of fetuin gene (AHSG) polymorphisms on the protein product and outcome. Methods: In a cohort 258 (161 males) ESRD patients starting renal replacement therapy [glomerular filtration rate (GFR) 6,8 +/- 0,2 mL/min] aged 52 +/- 1 years the following parameter were studied: presence of malnutrition (subjective global assessment), comorbidity (diabetes mellitus and clinical manifest cardiovascular disease (CVD)], carotid plaques (N = 101), hs-CRP, fetuin-A, S-albumin, interleukin (IL)-6, and single nucleotide polymorpisms (SNPs) in AHSG gene (N = 215) at amino acid positions Thr248Met (C -- >T), Thr256Ser (C -- >G), Asp276Asn (G -- >A), and Arg317Cys (C -- >T). Results: Both all cause (P < 0,001) and cardiovascular (P < 0,001) mortality were associated with low fetuin-A levels independently of age, smoking, diabetes, S-albumin, CVD, and inflammation (CRP > or = 10 mg/L). Inflammed (0,199 vs ,247 g/L; P < 0,01) and malnourished (0,207 vs 0,262 g/L; P < 0,05) patients had significantly lower median fetuin-A than noninflammed and well-nourished ESRD patients, respectively. In a logistic regression model N=101), fetuin-A was significantly (P < 0,05) associated with the presence of carotid plaques independently of age, CVD, diabetes, S-albumin, gender, and inflammation. Significant correlations were observed between fetuin-A and both S-albumin (Rho = 0,30; P < 0,0001) and IL-6 (Rho = 0,21; P < 0,01). Patients with AHSG 256Ser allele had lower serum fetuin-A levels, and higher all-cause and cardiovascular mortality rate if they were inflamed. Conclusion: The present study shows that a low fetuin-A level is associated with malnutrition, inflammation, and atherosclerosis (carotid plaques), as well as with increased cardiovascular and all-cause mortality. Because the present study demonstrates an effect variations in the AHSG gene on both circulating fetuin-A levels and outcome, this indicates that ESRD patients with the 256Ser allele are at risk of accelerated vascular calcification.

13. End-stage renal disease - not an equal opportunity disease: the role of genetic polymorphisms

Nordfors L Lindholm B, Stenvinkel P

J Intern Med 2005 258: 1-12.

Abstract Despite several decades of development in renal replacement therapy, end-stage renal disease (ESRD) patients continue to have markedly increased morbidity and mortality especially caused by cardiovascular disease (CVD). This shows that current strategies, e.g. the focus on dialysis adequacy, to improve the clinical outcome in ESRD patients have to be complemented by novel approaches. Although traditional risk factors are common in dialysis patients the cannot alone explained the unacceptably high prevalence of CVD in this patients group. Mich recent interest has therefore focused on the role of various nontraditionl crdiovascular risk factors, such as inflammation, vascular calcification and oxidative stress. Recent studies show that genetic factors, such as DNA single nucleotide polymorphisms, may significantly influence the immune response, the levels of inflammatory markers, as well as the prevalence of atherosclerosis in this patient group. To elucidate the respective roles of DNA polymorphisms in genes that encode inflammatory markers (such as IL-10 and TNF-alpha) and other factors that may affect the development of atherosclerosis (such as apolipoprotein E, transforming growth factor and fetuin-A), sufficiently powered studies are needed in which genotype, the protein product and the specific phenotype all are analysed in relation to outcome. The recent developments in the field of genetics have opened up entirely new possibilities to understand the impact of genotype on disease development and progress and thus offer new options and strategies for treatment. It seems conceivable that in the near future, prognostic or predictive multigene DNA assays will provide the nephrological

community with a more precise approach for the identification of 'high-risk' ESRD patients and development of accurate individual treatment strategies. For this purpose, integrative studies on-genotype-phenotype associations and impact on clinical outcome are needed.

14. Autoantibodies that bind glomeruli: cross-reactivity with bacterial antigen

Chowdhry IA, Kowal C, Hardin J et al.

Arthritis Rheum 2005 52 (8): 2403-16.

Abstract Objective: Systemic lupus erythematosus (SLE) is characterized by the production of multiple autoantibodies. Anti-DNA antibodies are associated with glomerulonephritis in SLE. It has been shown that anti-DNA antibodies cross-react with bacterial polysaccharide and, thus, might be elicited by microbial exposure. Non-DNA-binding antibodies also contribute significantly to the pathogenesis of lupus nephritis. The goal of this study was to characterize combinatorial library derived from spleen cells of a patient with SLE who had just previously received pneumococcal vaccine. The phage library was used in an in vivo biopanning technique to identify non-DNA-binding, kidney-binding antibodies. Antibodies were then analyzed for binding to bacterial polysaccharide and to renal antigens. Results: Eight antibodies were characterized that bound glomeruli, but not DNA. All antibodies isolated by this protocol were IgG class, suggesting that there is affinity maturation for glomerular binding. Four of the antibodies cross-reacted with pneumococcal polysaccharide. Six of the antibodies bound to renal antigens that have previously been reported to be cross-reactive with DNA; the other 2 bound to histone. Conclusion: This study suggest that both DNA-binding and non-DNA-binding antibodies in SLE may be elicited by the same bacterial antigens.

15. The interplay of chemokines and dendritic cells in the pathogenesis of lupus nephritis

Tucci M, Calvani N, Richards HB et al.

Ann N Y Acad Sci 2005 1051: 421-32.

Abstract Lupus nephritis (LN) occurs in more that one-third of patients with systemic lupus erythematosus. Production of nephritogenic autoantibodies, glomerular immunocomplex deposition, and cytokine overproduction have been postulated to contribute to the pathogenesis of LN. However, overexpression of chemokines and imbalance of dendritic cell (DC) homeostasis may contribute to the development of nephritis in SLE. We present evidence that monocyte chemoattractant protein (MCP)-1 promotes renal disease in experimental glomerulonephritis, while its increased urinary levels reflect the severity of the disease in humans. Athough macrophages are the prevalent infiltrating population within the kidney, it has been recently proposed that several chemokines and related receptors expressed by DCs may divide this cell population into myeloid (mDC) and plasmacytoid (pDC) subsets. However, the chemokine receptors expressed by pCDare not functional, and other molecules are involved in the chemoatrtraction of these cells. We found increased expression of interleukin (IL)-18 in glomeruli of patients with active LN along with glomerular infiltration by pCDs. Since pCDs bear IL-18 receptor (IL-18R), it is conceivable that circulating pCDs may migrate toward glomeruli by IL-18/IL-18R interactions. Therefore, the relative depletion of circulating pDCs reflects the severity of inflammatory disease in LN.

16. Familial small-vessel vasculitis of the kidney

Devaux JP, Kyndt X, Binaut R et al.

Presse Med 2005 34 (12): 861-2.

Abstract Introduction: Familial forms of small-vessel vasculitis has been reported in 14 families (including this one). Cases: A father and son were both diagnosed with renal

vasculitis (pauci-immune crescentic glomerulonephritis). Both had antimyeloperoxidase autonantibodies, and there was no evidence of a common environmental factor. Discussion: These cases suggest the role of constitutional factors in the pathogenesis of antineutrophil cytoplasmic antibody-associated vasculitis.

17. Goodpasture autoantibodies unmask cryptic epitopes by selcetively dissociating autoantigen complexes lacking structural reinforcement: novel mechanisms for immune privilege and autoimmune pathogenesis

Borza DB, Bondar O, Colon S et al.

J Biol Chem 2005 280 (29): 27147-54.

Abstract Rapidly progressive glomerulonephritis in Goodpasture disesase is mediated by autoantibodies binding to the non-collegenous NC1 domain of alpha3(IV) collagen in the glomerular besement membrane. Goodpasture epitopes in the native autoantigen are cryptic (sequestered) within the NC1 hexamers of the alpha3/alpha4/alpha5(IV) collagen network. The biochemical mechanism for crypticity and exposure for autoantibody binding is not known. We now report that crypticity is a feature of the quaternary structure of two distinct subsets of alpha3/alpha4/alpha5(IV) NC1 hexamers: autoantibody-reactive M-hexamers containing only monomer subunits and autoantibody-impenetrable D-hexamers composed of both dimer and monomer subunits. Goodpasture antibodies only breach the quaternary structure of M-hexamers, unmasking the cryptic epitopes, whereas D-hexamers are resistant to autoantibodies under native conditions. The epitopes of D-hexamers are structurally sequestered by dimer reinforcement of the quaternary complex, which represents a new molecular solution for conferring immunologic privilege to a potential autoantigen. Dissociation of non-reinforced M-alpha3/alpha4/alpha5(IV) hexamers by Goodpasture antibodies is a novel mechanism whereby pathogenic autoantibodies gain access to cryptic B cell epitopes. These findings provide fundamental new insights into immun privilege and the molecular mechanisms underlying the pathogenesis of human autoimmune Goodpasture disease.

18. Avidity of anti-glomerular basement membrane autoantibodies was associated with disease severity

Cui Z, Zhao MH

Clin Immunol 2005 116 (1): 77-82.

Abstract Anti-glomerular basement membrane (GBM) antibody mediated diseases are characterized by the binding of autoantibodies to GBM, leading to rapidly progressive glomerulonephritis that often results in irreversible loss of renal function. The nephrotoxic potential of anti-GM antibodies has been demonstrated in animal experiments. We questioned wether high avidity leads to peristent deposition of anti-GBM antibodies, thereby perpetuating inflammation and renal damage. To adress the hypothesis, sera from 32 patients and serial samples from 11 patients with ani-GBM disease were collected. Purified bovine alpha chain non-collagen 1 domains of type IV collagen [alpha (IV) NC1] were employed to exam avidity to anti-GBM antibodies using antigen-inhibition enzyme-linked immunosorbent assay. The amount of alpha(IV)NC1 needed for 50% inhibition of antibody binding was compared among patients with different clinical and pathological parameters. After the sera were diluted to give equivalent concentration of anti-GBM antibodies, the amoint of alpha(IV)CN1 used for 50% inhibition was prominently different among patients, from 0,02 microg to 20 microg, with an average at 0,666 microg. A significant correlation was observed between the amount of alpha (IV)NC1used and the percentage of glomeruli which had crescents(P=0,001). Higher avidity of anti-BGM antibodies predicted higher percentage of glomerular crescents (R2=0,58, P<0,001). No obvious change of avidity was observed in the serial samples. The results suggested that affinity maturation might have been completed by the time that patients presented with anti-GBM disease. The avidity of anti-GBM antibodies was associated with the degree of renal damage and might play a key role in the pathogenesis of anti-GBM disease.

19. ANCA-negative pauci-immune renal vasculitis: histology and outcome

Eisenberger U, Fakhouri F, Vanhille P et al.

Nephrol Dial Transplant 2005 20: 1392-9.

Abstract Background: Pauci-immune renal vasculitis with focal glomerular necrosis and crescent formation is usually associated with anti-neutrophil cytoplasmic antibodies (ANCAs). However, ANCA's are absent in up to 10% of cases, which consitutes a rarely studied variant of renal vasculitis. Methods: This retrospective multicentre cohort study analyzed the presenting features, renal histology and outcome in 20 patients with pauci-immune crescentic necrotizing renal vasculitis in whom indirect immunofluorescence did not detect ANCA. Results: Renal histology revealed a high percentage of active glomerular lesions (50%), mainly cellular crescents, 28% of them with glomerular necrosis. Chronic tissue damage with glomerulosclerosis (21%) and diffuse interstitial fibrosis (40%) was already present at diagnosis, more prominent than in historical PR3-positive patients. Infiltrates of polymorpnuclear neutrophils in glomerular capillary loops were observed in 40% of all biopsies, mainly in necrotic lesions. The subsets of interstitially infiltrating leukocytes similar to ANCA-associated disease. Microscopic polyangiitis was diagnosed in 17 patients, Wegener's granulomatosis in two and renal-limited vasculitis in one. The patients median disease extent index (DEI) of 5 (range 4-11) reflected a systemic vasculitis. ANCA-negative vasculitis was not associated with infection or malignancy. Renal outcome was correlated to DEI (P=0,032) and serum creatinine at diagnosis (P=0,04). The mortality rate was high (3%) and closely related to age above 65 years at diagnosis (P=0,014). Conclusions: The histological findings and prognosis in ANCA-negative renal vasculitis are comparable with those of ANCA-positive disease. Our data underline importance of the exact diagnosis in an active vasculitic disease process in the absence of ANCAs.

20. Alport syndrome in southern Sweden

Persson U, Hertz JM, Wieslander J et al.

Clin Nephrol 2005 64 (2): 85-90.

Summary: See Part 2/EP/5

21. TRPC6 is a glomerular slit diaphragm-associated channel required for normal renal function

Reiser J, Polu KR, Moller CC et al.

Nat Genet 2005 37 (7): 739-44.

Abstract Progressive kidney failure is a genetically and clinically heterogeneous group of disorders. Podocyte foot processes and the interposed glomerular slit diaphragm are essential components of the permeabilty barrier in the kidney. Mutations in genes encoding structural proteins of the podocyte lead to the development of proteinuria, resulting in progressive kidney failure and focal segmental glomerulosclerosis. Here, we show that the canonical transient receptor potential 6 (TRPC6) ion channel is expressed in podocytes and is acomponent of the glomerular slit diaphragm. We identified five families with autosomal dominant focal segmental glomerulosclerosis in which disease segregated with mutations in the gene TRPC6 on chromosome 11q. Two of the TRPC6 mutants had increased current amplitudes. These data show that TRPC6 channel activity at slit diaphragm is essential for proper regulation of podocyte structure and function.

22. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis

Winn MP, Conlon PJ, Lynn KL et al.

Science 2005 308 (5729): 1801-4.

Abstract Focal and segmental glomerulosclerosis (FSGS) is a kidney disorder of unknown etiology, and up to 20% patients on dialysis have been diagnosed with it. Here we show that a large family with hereditary FSGS carriers a missense mutation in the TRPC6 gene on chromosome 11q, encoding the ion-channel protein transient receptor potential cation channel 6 (TRPC6). The proline-to-glutamine substitution at position 112, which occurs in a highly conserved region of the protein, enhances TRPC6-mediated calcium signals in response to agonists such as angiotensin II and appears to alter the intracellular distribution of TRPC6 protein. Previous work has emphasized the importance of cytoskeletal and strutural proteins in proteinuric kidney diseases. Our findings suggest an alternative mechanism for the pathogenesis of glomerular disease.

23. IgA: an immune glycoprotein

Yoo EM, Morrison SL

Clin Immunol 2005 116 (1): 3-10.

Abstract IgA is a glycoprotein containing multiple N-linked carbohydrates as well as O-linked glycans in the case of IgA1. Because of the critical role it plays in providing protection at mucosal surfaces, IgA is an ideal candidate for use as a therapeutic or prophylactic agent. The presence or absence of carbohydrates, as well as their structure, has been found to influence effector functions and binding to specific IgA receptors. In addition, changes in IgA glycolisation are associated with immune pathology. A through understanding of the contributions of the glycans to IgA immun protection will aid in the design of clinically suitable antibodies.

24. Aberrantly glycolisated serum IgA1 are closely associated with pathologic phenotypes of IgA nephropathy

Xu LX, Zhao MH

Kidney Int 2005 68 (1): 167-72.

Abstract Background: IgA nephropathy (IgAN) is the most common glomerulonephritis with various histologic and clinical phenotypes. The mechanisms underlying the pathogenesis of IgAN remained unclear. But now altered O-glycosylation of serum IgA1 observed in these patients was considered to be a key contribution factor. The aim of the current study is to investigate whether aberrantly glycosylated IgA1 was associated with pathologic phenotypes of IgAN. Methods: Sera from 107 patients with IgAN recently diagnosed were collected. Fifty patients were with mild mesangial proliferative IgAN, the others were with focal proliferative and sclerosing IgAN. Sera from 22 normal blood donors were used as normal controls. Biotinylated lectins were used in enzyme-linked immunosorbent assay (ELISA) to examine different glycans on IgA1 molecules. The alpha2,6 sialic acid was detected by elderberry bark lectin (SNA), the exposure of terminal galactose (Gal) and N-acetylgalactosamine (Ga1Nac) were detected by arachis hypogaea [penaut agglutinin (PNA)] and vilsa villosa lectin (VVL), respectively. The serum IgA1 glycans levels corrected by serum IgA1 concentrations were compared between patients and controls. Results: Reduced terminal alpha2,6 sialic acid (1,16 +/- 0,21 vs ,98 +/- 0,31) (P=0,008) and galactosylation (0,30 +/- 0,29 vs 0,16 +/- 0,19) (P=0,029) increased exposure of (Ga1Nac) (0,00 vs 0,03) (P=0,024) were demonstrated in serum IgA1 from patients with IgAN as compared with those controls. More important, the exposure of 2,6 sialic acid and Gal were significantly decreased, espacially in patients with focal proliferative and sclerosing IgAN compared with that in patients with mild mesangial proliferative IgAN (0,91 +/- 0,34 vs 1,05 +/- 0,25) (P=0,014) (0,108 +/- 0,137 vs 0,221 +/- 0,219) (P=0,018). However, no significant differece was found between patients with mild mesangial proliferative IgAN and normal controls (P > 0,05). The exposure of Ga1Nac of

serum IgA1 from patients with focal proliferative and sclerosing IgAN was significantly higher thanm that of controls (P=0,017), but had no statistical difference with that of patients with mild mesangial proliferative IgAN. Conclusion: The desialylation and degalactosylation of IgA1 in sera of patients with IgAN were closely associated with pathologic phenotypes.

25. Molecular basis of IgA nephropathy

Lai AS Lai KN

Curr Mol Med 2005 5 (5): 475-87.

Abstract IgA nephropathy (IgAN) is the most glomerulonephritis worldwide and remains an important cause of end-stage renal failure. However, the basic molecular mechanism(s) underlying abnormal IgA synthesis, selective mesangial deposition with ensuing mesangial cell proliferation and extracellular matrix expansion remains poorly understood. Notably, the severity of tubulointerstitial lesions better predicts the renal progression than the degree of glomerular lesions. The task of elucidating the molecular basis of IgAN is made especially challenging by the fact that both environmental and genetic components likely contribute to the developmnet and progression of IgAN. This review will summarize the earlier works on the structure of the IgA molecule, mechanisms of mesangial IgA deposition and pathophysiologic effects of IgA on mesangial cells following mesangial deposition. Recently, a series of important advances in the area of communication between the glomerular mesangium and renal tubular cells have emerged. These novel findings regarding the molecular pathogenesis of IgAN will be helpful in designing future directions for therapy.

26. Engagement of Transferrin Receptor by Polymeric IgA1: Evidence for Positive Feedback Loop Involving Increased Receptor Expression and Mesangial Cell Proliferation in IgA nephropathy

Moura IC, Arcos-Fajardo M, Gdoura A et al.

J Am Soc Nephrol 2005 16 (9): 2667-76.

Abstract The transferrin receptor (TfR) was identified previously as an IgA1 receptor, and it was found that, in biopsies of patients with IgAN, TfR is overexpressed and co-localizes with IgA1 mesangial deposits. Here, it is shown that purified polymeric IgA1 (pIgA1) is a major inducer of TfR expression (three- or four-fold increase) in quiescent human mesangial cells (HMC). IgA-induced but not cytokine-induced HMC proliferation is dependent on TfR engagement as it is inhibited by both TfR1 and TfR2 ectodomains as well as by the anti-TfR mAb A24. It is dependent on the continued presence of IgA1 rather than on soluble factors released during IgA1-mediated activation. In addition, pIgA1-induced IL-6 and TGF-beta production from HMC was specifically inhibited by mAb A24, confirming that pIgA1 triggers a TfR-dependent HMC activation. Finally, upregulation of TfR expression induced by sera from patients with IgAN but not from healthy individuals was dependent on IgA.- It is proposed that deposited pIgA1 or IgA1 immuno complexes could initiate a process of auto-amplification involving hyperexpression of TfR, allowing increased IgA1 mesangial deposition. Altogether, these data unveil a functional cooperation between pIgA1 and TfR for IgA1 dposition and HMC proliferation and activation, features that are commonly implicated in the chronicity of mesangial injuries observed in IgAN and that could explain the recurrence of IgA1 deposits in the mesangium after renal transplantation.

27. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy

Honkanen T, Mustonen J, Kainulainen H et al.

Kidney Int 2005 67 (6): 2187-95.

Abstract Background: Clinical manifestation of IgA nephropathy (IgAN) strikingly ocurs after respiratory tract infections. An interstitial inflammation has also been described. We hypothesized that the intestinal inflammation should manifest itself as an increase in inflammatory cells and mucosal cyclooxygenase 2 (COX-2) expression. Methods: By using immunohistochemistry, we determined the phenotype and quantity of inflammatory cells in duodenal biopsy specimens from 17 IgAN patients. Control material comprised 18 patients undergoing gastroscopy because of dyspepsia. Results: All biopsy specimens disclosed normal villous architecture. In IgAN, CD3(+) cells and COX-2-positive cells were significantly increased and J chain-producing plasma cells were significantly decreased.CD3(+) cells coexpressed COX-2 protein and COX-2-positive cells also expressed CD45RO antigen. The number of lymphocytes correlated significantly with serum IgA and COX-2-expression with serum IgA and the degree of hematuria. COC-2-positive subepithelial fibroblasts were a conspicuous finding in IgAN. In CD68(+) and CD15(+) cells, a significant increase was seen: Many of these cells also expressed COX-2 protein: CD15(+) positivity correlated significantly with proteinuria in IgAN. Conclusion: Our results indictae that small bowel inflammation in IgAN shows itself as an increased number of mucosal inflammatory cells. However, polymeric IgA production is significantly decreased. An increased mucosal COX-2 expression suggest activation of the inflammatory cells and degree of inflammation significantly correlates with serum IgA and the amount of proteinuria and hematuria. Subepithelial fibroblasts seem also to be involved in the inflammatory reaction.

28. Pathogenic mechanisms in membranoproliferative glomerulonephritis

Smith KD, Alpers CE

Curr Opin Nephrol Hypertens 2005 14 (4): 396-403.

Abstract Purpose of Review: This review considers new information on the pathogenesis of a long recognized and poorly understood form of glomerular injury, membranoproliferative glomerulonephritis. This disease has received growing attention as it is the principal renal manifestation of hepatitis C virus infection, which has become pandemic worlwide. Recent Findings: This review briefly describes three murine models of membranoproliferative glomerulonephritis suitable for pathogenesis studies. We consider recent evidence implicating innate immune mechanisms in immune and autoimmune-mediated glomerulonephritis, and recent data pointing to the alternative pathway of complement activation in the amplification of glomerulonephritic injury. Summary: Understanding the contribution of complement activation and innate immunity to the evolution of membranoproliferative glomerulonephritis promises to provide new therapeutic targets for this disease. Inhibitors of the complement cascade are already being tested in clinical trials as therapeutic interventions for some human glomerular disease. Successful tests of this approach in membranoproliferative glomerulonephritis are still awaited. Our understanding of the innate immune system modulates glomerulonephritis is still in an early stage, and future studies should be directed at identifying targets and specific interventions that may also benefit patients with this disease.

29. Aldose reductase in diabetic microvascular complications

Chung SS, Chung SK

Curr Drug Targets 2005 6 (4): 475-86.

Abstract Most long-term diabetic patients develop microvascular diseases such as retinopathy, nephropathy and neuropathy. Although tight control of blood glucose greatly reduces the incidence of these complications, a significant fraction of diabetic patients with good glycemic control still develop these diseases. Therefore, it is imperative to understand the underlying mechanisms of these disease such effective treatment or preventive methods can be developed to augment euglycemic control. In animal studies, there is strong evidence that aldose reductase, the first and rate-limiting enzyme of the polyol pathway that converts glucose to fructose, plays a key role in the pathogenesis of microvascular complications. However, clinical trials of the aldose reductase inhibitors were disappoining and several

pharmaceutical companies had abandoned the development of this line of drugs. In this review, the potential pathogenic mechanisms of the polyol pathway are presented, the evidence for the involvement of the polyol pathway in diabetic complications summarized, and the reasons for the unimpressive results of the clinical trials of the aldose inhibitors discussed. It appears that renewed efforts to develop aldose reductase inhibitors for the treatment and prevention off diabetic complications are warranted.

30. Role for poly(ADP-ribose) polymerase activation in diabetic nephropathy, neuropathy and retinopathy

Obrosova IG, Julius UA

Curr Vasc Pharmacol 2005 3 (3): 267-83.

Abstract Chronic complication of diabetes mellitus e.a. diabetic nephropathy, neuropathy and retinopathy develop in at least 30-50% of patients both Type 1(insulin dependent) and Type 2 (non-insulin-dependent) diabetes, and are the major cause of increased morbidity and mortality. The ultimate consequences of diabetes complications include renal failure, foot ulceration and amputation and blindness. The magnitude of the problem and its economic impact make extremely important to understand the natural history of chronic diabetes complictions and to identify more successful prevention and therapeutic options. The pathogenesis of diabetes complications involve multiple mechanisms. The importance of vascular component is well recognized in diabetic retinopathy, which is primarily a vascular disease, as well as diabetic nephropathy developing as a result of complex interplay between hemodynamic and metabolic factors. The importance of vascular versus non-vascular mechanisms in the pathogenesis of diabetic neuropathy remains a subject of debate. Studies in animal and cell culture models revealed that such mechanisms as increased aldose reductase activity, non-enzymatic glycation/glycoxidation, activation of protein kinase C, impaired growth factor support, enhanced oxidative/nitrosative stress, and its downstream effectors such as mitogen-activated protein kinase activation, inflammatory response, endothelin-1 overexpression and impaired Ca(++) signaling, play an important role in all three tissue-targets for diabetes complication i.e. kidney, retina and peripheral nerve. Evidence for important role of the downstream effector of free radical and oxidant-induced DNA injury, poly(ADP-ribose) polymerase activation, is emerging. This review describes recent studies addressing the role for poly(ADP-ribose) polymerase activation in diabetic nephropathy, neuropathy and retinopathy.

31. From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy

Wolf G, Chen S, Ziyadeh FN

Diabetes 2005 54 (6): 1626-34.

Abstract Nephropathy is a major complication of diabetes. Alteration of mesangial cells have traditionally been the focus of research in deciphering molecular mechanisms of diabetic nephropathy. Injury of podocytes, if recognized at all, has been considered a late consequence caused by increasing proteinuria rather than an event inciting diabetic nephropathy. However, recent biopsy studies in humans have provided evidence that podocytes are functionally and structurally injured very early in the natural history of diabetic nephropathy. The diabetic millieu, represented by hyperglycemia, nonenzymatically glycated proteins, and mechanical stress associated with hypertension, causes downregulation of nephrin, an important protein of the slit diapragm with antiapoptotic signaling properties. The loss of nephrin leads to foot process effacement of podocytes and increased proteinuria. A key mediator of nephrin suppression is angiotensin II (ANG II), which can activate other cytokine pathways such as transforming growth factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF) systems. TGF-beta causes an increase in mesangial matrix deposition and glomerular basement membrane (GBM) thickening and may promote podocyte apoptosis or detachment. As a result, the denuded GBM aheres to Bowman1s capsule, initiating the development of

glomerulosclerosis. VEGF is both produced by an acts upon the podocyte in an autocrine manner to modulate podocyte function, including the synthesis of GBM components. Through its effects on podocyte biology, glomerular hemodynamics, and capillary endothelial permeability, VEGF likely plas an important role in diabetic albuminuria. The mainstays of therapy, glycemic control and inhibition of ANG II, are key measures to prevent early podocyte injury and the subsequent of diabetic nephropathy.

32. Poly(ADP-ribose) polymerase-mediated cell injury in acute renal failure

Devalaraja-Narshimha K, Singaravelu K, Padanilam BJ

Pharmacol Res 2005 52 (1): 44-59.

Abstract Acute Renal Failure (ARF) is the most costly kidney disease in hospitalized patients and remains as a serious problem in clinical medicine. The mortality rate among ARF patients remains around 50% and no pharmaceutical agents are currently available to improve its clinical outcome. Although several successful therapeutic approaches have been developed in animal models of the disease, translation of the results to clinical ARF remains elusive. Understanding the cellular and molecular mechanisms of vascular and tubular dysfunction in ARF is important for developing acceptable therapeutic interventions. Following an ischemic episode, cells of the affected nephron undergo necrotic and/or apoptotic cell death. Necrotic cell death is widely considered to be a futile profess that cannot be modulated by pharmacological means as opposed to apoptosis. However, recent reports from various laboratories including ours indicate that inhibition or absence of poly(ADP)-ribose polymerase (PARP), one of the molecules involved in cell death, provides remarkable protection in disease models such as stroke, myocardial infarction and renal ischemia which are characterized predominantly by necrotic type of cell death. Overactivation of PARP in conditions such as ischemic renal injury leads to cellular depletion of its substrate NAD+ and consequently ATP. The severely compromised cellular energetic state induces acute cell injury and diminishes renal functions. PARP activation also enhances the expression of proinflammatory agents and adhesion molecules in ischemic kidneys. Pharmacological inhibition and gene ablation of PARP-1 decreased energy depletion, inflammatory response and improved renal functions in the setting renal ischemia/reperfusion injury. The biochemical pathways and cellular and molecular mechanisms mediated by PARP-1 activation in eliciting the energy depletion and inflammatory responses in ischemic kidney are not fully elucidated. Dissecting the molecular mechanisms by which PARP activation contributes to oxidant-induced cell death will provide new strategies to interfere in those pathways to modulate cell death in renal ischemia. The current review evaluates the experimental evidences in animal and cell culture models implicating PARP as a pathophysiological modulator of acute renal failure with particular emphasis on ischemic renal injury.

33. Lights and shadows on the pathogenesis of contrast induced nephropathy: state of the art

Detrenis S, Meschi M, Musini S et al.

Nephrol Dial Transplant 2005 20: 1542-50.

Abstract The aim of this paper was to review the complex mosaic of medical literature that discusses the pathophysiology of the contrast media-induced nephropathy (CMIN), when possible by considering analogies with nephropathies of better-known pathogenesis, and without the pretension to reach any containties or to dictate any interpretations. Considering the fact that multiple biopsies or invasive examinations are for the most part not feasible or ethically acceptable in humans, it may be a long time before definitive and indisputable answers are found regarding the pathogenic mechanisms of CMIN, although clinical findings on an adequate number of homogenous patient populations may provide better insights to the problem. At present, our knowledge concerning renal damage due to radiocontrast agents is still limited since it is affected by a partial vision of the problem. A good history of individual patients at risk, the efficient correction of alterations due to background disease, the detection and correection of dehydration and prophylactic abundant hydration where fluid

overload is not contraindicated represent the true preventive measures of CMIN that are available in the year 2005, since pharmacological prophylaxis has proven to be unreliable.

34. Peritubular capillary injury in Chinese herb guan-mu-tong-induced acute tubular necrosis

Yang L, Li XM, Wang SX et al.

Zhonghua Nei Ke Za Zhi 2005 44 (7): 525-9.

Summary: See Part 2/ET/12

IV. CLINICAL PRESENTATION

1. Relationship of gender, age, and body mass index to errors in predicted kidney function

Cirillo M, Anastasio P, De Santo NG

Nephrol Dial Transplant 2005 20: 1791-8.

Abstract Background: Previous studies have shown conflicting data on accuracy of equations for kidney function prediction. The present work analysed the relationship of gender, age and body mass index (BMI) to error of predictions by the Cockcroff-Gault equation (Cg_{eq}), the simplified equation of the Modification of Renal Diseases Study ($MDRD_{eq}$) and the Mayo Clinic equation ($Mayo_{eq}$). Methods: Inulin clearence (glomerular filtration rate; GFR) and other variables were measured in 380 subjects of both sexes, aged 18-88 years, with and without kidney disease. GFR was defined as low when <60ml/minx1,73m^ 2. BMI was used for definition of underweight/overweight. Relative error of predictions was used as an index for bias. It was claculated as prediction minus GFR (positive values=overestimates, negative values=underestimates) and expressed as a percentage of the GFR. Absolute error was used as an index of imprecision and was calculated as absolute value of relative error. Results: CG_{eq} relative error was inversely associated with age and directly associated with BMI (p<0,001), but not with gender or GFR. $MDRD_{eq}$ relative error was inversely associated with female gender and GFR (p<0,001), but not with age or BMI. $Mayo_{eqw}$ relative error was directly associated with male gender, BMI, and GFR (p<0,01), but not with age. Absolute error was higher for Cg_{eq} than for $MDRD_{eq}$ but only at low GFR (p<0,001). $Mayo_{eq}$ had a higher absolute error than Cg_{eq} and $MDRD_{eq}$ (p<0,01). Conclusion: Errors of predictions varied not only with GFR but also with gender, age and BMI. Without using creatinine assay calibration, $Mayo_{eq}$ was less accurate than both $MDRD_{eq}$ and Cg_{eq} , whereas $MDRD_{eq}$ was slightly more precise than Cg_{eq} but only at low GFR.

2. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition

Lositi A, Errico R, Santirosi P et al.

Nephrol Dial Transplant 2005 20: 1604-9.

Abstract Background: Patients with atherosclerotic renovascular disease (ARVD) are almost invariably treated by revascularization. However, the long-term outcomes of this approach on survival and progression to renal failure not been investigated and have not been compared with that of a purely medical treatment. The aim of this observational study was to investigate factors affecting long-term (over 5 years) outcome, survival and renal function of patients with ARVD treated invasively or medically. Methods: ARVD was demonstrated angiographically in 195 patients who were consecutively enrolled into a follow-up study. Patient age was 65,6± 11,2 years, serum creatinine was 1,74± 1,22mg/dl and renal artery lumen narrowing was 73,5± 17,5%. A revascularization was performed in 136 patients, whereas 54 subjects having comparable characteristics were maintained on a medical treatment throughout the study; five patients were lost during follow-up. Results: The main follow-up was 54,4± 40,4 months. The assessment of cardiovascular survival and renal survival at the end of follow-up revealed 46 cardiovascular deaths, 20 patients with end-stage renal disease (ESRD) and 41 patients with an increase in serum creatinine of over one-third. The multivariate analysis showed that renal revascularization did not affetc mortality or renal survival compared with medical treatment. Revascularization produced slightly lower increases in serum creatinine and a better control of blood pressure. A longer survival was associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) (p=0,002) in both revascularized and medically treated patients. The only significant predictor of ESRD was an abnormal baseline serum creatinine. Conclusion: On long-term follow-up, ARVD was associated with a poor prognosis due to a high cardiovascular mortality and a high rate of

ESRD. In our non-randomized study, revascularization was not a major advantage over medical treatment in terms of mortality or renal survival. The use of ACEIs was associated with improved survival.

3. A Japanese family with Alport syndrome associated with esophageal leiomyomatosis: genetic analysis of COL4A5 to COL4A6 and immunostaining for type IV collagen subtypes

Sugimoto K, Yanagida H, Yagi K et al.

Clin Nephrol 2005 64 (2): 144-50.

Abstract Background: In some families X-linked Alport syndrome (AS) is associated with diffuse leiomyomatosis. We describe clinical, pathologic and molecular-genetic findings in a Japanese family with this inheritance mode of AS in association with leiomyomatosis. Patient: AS was diagnosed in a one-year-old boy with recurrent aspiartion pneumonia caused by esophageal stenosis from leiomyomatosis. Diagnosis was confirmed by electron microscopy coupled with type IV collagen chain subtype staining in a renal biopsy specimen. His mother, who exhibited esophageal leiomyomatosis and is heterozygous for AS, showed a discontinuous staining pattern for collagen alpha5(IV) chain along the epidermal basement membrane in a skin biopsy specimen. Genetic analysis in the boy revealed the deletion of the first two exons of COL4A6 together with deletion of the 5' and of COL4A5. Despite administration of cyclosporin A, massive proteinuria has persisted in the boy, although renal function otherwise remains normal. Conclusion: Identification of an AS patient during infancy is extremely rare. Clinical manifestations, including macroscopic hematuria, cataracts and leiomyomatosis caused by the large deletion involving COL4A5 to Col4A6, led to early presentation with AS.

4. Sarcoid granulomatous interstitial nephrits and sarcoid abdominal aortic aneurisms

Hatta T, Tanda S, Kusaba T et al.

Nephrol Dial Transplant 2005 20: 1480-2.

Summary: See Part 2/ET/9

5. Glomerulonephritis associated with acute pneumococcal pneumonia: a case report.

Phillips J, Palmer A, Baliga R

Pediatr Nephrol 2005 Jul 12 [Epub ahead of print]

Summary: See Part 2/ET/1

6. Familial Mediterranean fever and mesangial proliferative glomerulonephritis: report of a case and review of the literature

Cagdas DN, Gucer S, Kale G et al.

Pediatr Nephrol 2005 20 (9): 1352-4.

Summary: See Part 2/ET/6

7. Relapse of lupus nephritis more than 10 years after complete remission

Carlavilla A, Gutiérrez E, Ortuno T et al.

Nephrol Dial Transplant 2005 20: 1994-8.

Abstract Over the last decade there has been a dramatic improvement in the treatment and prognosis of lupus nephritis, even in its most severe forms. However, most investigations have focused mainly on the initial episodes of lupus nephritis. Information about the treatment of relapses or the correct long-term management of clinically quiescent patients is relatively scarce. These aspects are particularly important because current therapeutic options allows renal survival after the first episode of lupus nephritis in a majority of patients and because clinical studies have shown that recurrent renal fleres are common: 37-45% of patients successfully treated at their initial episode have relapses of nephritis later. Most of these relapses occur soon after the initial episode, especially when immunosuppressive therapy is reduced. Since the risk of very late relapse appears to be very low, complete discontinuation of immunosuppressive therapy has been advocated in selected patients with quiescent lupus. However, we report here four patients with diffuse lupus nephritis who had relapses more than 10 years after complete remission.

8. Antiphospholipid syndrome: review

Sammaritano LR

South Med J 2005 98 (6): 617-25.

Abstract Antiphospholipid syndrome spans many medical disciplines. Classic criteria include the presence of anticardiolipin antibody or lupus anticoagulant with typical complications of thrombosis or pregnancy loss. Other common associated manifestations include livedo reticularis, thrombocytopenia, valvular heart disease, and nephropathy with renal insufficiency, hypertension and proteinuria. Treatment of serious complications with anticoagulation is standard; generally warfarin for thrombosis and aspirin/heparin for pregnancy prophylaxis. Detailed recommendations regarding precise intensity and duration of anticoagulation are still a subject of debate.

9. Pulmonary alveolar hemorrhage in a pregnancy complicated by systemic lupus erythematosus

Gaither K, Halstead K, Manson TC

J Natl Med Assoc 2005 97 (6): 831-3.

Abstract We present a case of a pregnant patient with fulminant systemic lupus erythematosus complicated by alveolar hemorrhage, a rare and potentially fatal manifestation of lupus. It typically presents in the context of a pulmonary-renal syndrome. Active lupus nephritis with hypoalbuminemia is a major risk factor for alveolar hemorrhage. Treatment with high-dose corticosteroids is the manstay of therapy.

10. Expanding the pathologic spectrum of light chain deposition disease: a rare variant with clinical follow-up of 7 years

Chang A, Peutz-Kootstra CJ, Richardson CA et al.

Mod Pathol 2005 18 (7): 998-1004.

Summary: See Part 2/PG/8

11. Antineutrophil cytoplasmic antibodies (ANCA)

Radice A, Sinico RA

Autoimmunity 2005 38 (1): 93-103.

Abstract Antineutrophil cytoplasmic antibodies (ANCA) are a sensitive and specific marker for ANCA-associated systemic vasculitis. Using indirect immunofluorescence on ethanol-fixed neutrophils, two major fluoroscopic patterns can be recognised: a diffuse cytoplasmic staining (C-ANCA), and a perinuclear/nuclear staining (P-ANCA). In patients with vasculitis, more of 90% of C-ANCA are directed against protease 3 (PR3-ANCA) whereas approximately 80-90% of P-ANCA recognise myeloperoxidase (MPO-ANCA). Although C-ANCA (PR3-ANCA) is preferntially associated with Wegener's granulomatosis (WG), and P-ANCA (MPO-ANCA) with microscopic polyangiitis (MPA), idiopathic necrotizing crescentic glomerulonephritis (iNCGN) and Churg-Strauss syndrome (CSS), there is not absolute specificity. Between 10-20% of patients with classical WG show P-ANCA, and even a larger percentage of patients with MPA or CSS have C-ANCA (PR3-ANCA). Furthermore, it should be stressed that approximately 10-20% of patients with WG or MPAs of CSS) have negative assay for ANCA. The best diagnostic performance is obtained when indirect immunofluorescence is combined with PR3 and MPO-specific ELISAs. ANCA with different and unknown antigen specificity are found in a variety of conditions other than ANCA-associated systemic vasculitis (AASV), including inflammatory bowel diseases (IBD), other autoimmune diseases, and infectious where their clinical significance is unclear. ANCA levels are useful to monitor disease activity but should not be used by themselves to guide treatment. A significant increase in ANCA titres, or the reappearance of ANCA should alert the clinicians and lead to a stricter patient control.

12. Update on Wegener granulomatosis

Langford CA

Cleve Clin J Med 2005 72 (8): 689-90.

Abstract Wegener granulomatosis classically involves clinical disease of the upper airways, lungs, and kidneys. Ninety percent of patients present symptoms involving the upper or lower airways, or both, and it should be suspected in any patients with pulmonary hemorrhage, glomerulonephritis, mononeuritis multiplex, unexplained multisystem disease, or progressive unresponsive sinus disease. Current treatments induce remission and allow long-term survival.

13. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis

Rutgers A, Slot M, van Paassen P et al.

Am J Kidney Dis 2005 46 (2): 253-62.

Abstract Background: In a substantial proportion of patients with crescentic glomerulonephritis (CGN), both anti-glomerular basement membrane (GBM) antibodies and antineurophil cytoplasmic antibodies (ANCAs) with specificity for myeloperoxidase (MPO-ANCA) are detected. In the present study, we questioned whether histological and clinical features of patients with both ANCA and anti-GBM antibodies differ from those of patients with either ANCA or anti-GBM alone. Methods: We reviewed the Limburg renal biopsy registry (1978 to 2003; n = 1,373) for cases of CGN. The presence of linear fluorescence on renal biopsy and the presence of ANCA and/or anti-GBM were measured. Subsequently, we assessed patient characteristics and follow-up compared histological findings among the different groups. Results: We identified 46 MPO-ANCA positive, 10 double-positive, and 13 anti-GBM-positive patients. Mean ages were 63, 64, and 52 years (P = 0,04), and serum creatinine levels were 5.0, 10.3, and 9.6 mg/dL (445, 910, and 850 micromol/L), respectively (P = 0,01). Granulomatous periglomerular inflammation was found in either MPO-ANCA- or double-positive patients, but not in anti-GBM-positive patients with CGN without MPO-ANCAs. Patient survival among the 3 groups was different, although not statistically significant (10g rank P = 0.17, with 75%, 79%, and 100% alive at 1 year, respectively). Renal survival analysis showed significant differences among the 3 groups (P = 0,04, with 65%, 10%,

and 15% off dialysis therapy at 1 year, respectively). Conclusion: In patients with both anti-GBM antibodies and MPO-ANCAs, histological findings differ from those of patients with anti-GBM antibodies only. However, renal survival in these patients is not better than that in anti-GBM-positive patients and is worse compared with patients with MPO-ANCAs only.

14. Glomerulonephritis due to antineutrophil cytoplasm antibody-associated vasculitis: An update on approaches to management

Little MA, Pusey CD

Nephrology (Carlton) 2005 10 (4): 368-76.

Summary: A patient with antineutrophil cytoplasm antibody-associated vasculitis frequently has multisystem disease and might present to a range of medical specialities. The manifestations that results in the greatest burden of morbidity and mortality are renal and pulmonary disease. In this review we will focus on rapidly progressive glomerulonephritis due to vasculitis, with specific reference to recent advances in our understanding of pathogenesis. The current standard of care manging renal vasculitis, be it mild, moderate or severe, has largely been estabilished in clinical trials of prednisolone, cyclophosphamide, methotrexate, azathioprine and plasma exchange. In addition to these, newer therapies such as mycophenolate mofetil and infliximab are being used more frequently. We will review the role of each of these approaches to management of small vessel vasculitis in 2005.

15. Palisading neutrophilic granulomatous dermatitis in Japanese patients with Wegener's granulomatosis

Kawakami T, Obara W, Soma Y et al.

J Dermatol 2005 32 (6): 487-92.

Abstract Wegener's granulomatosis (WG) is an etiologically obscure entity with multiple systemic manifestations. Recently, cytoplasmic anti-neutrophil cytoplasmic antibody antibody (C-ANCA) has become recognized as a valuable adjunct in the diagnosis of this disorder. WG typically involves the upper airway, lungs, and kidneys, but any other organ can be involved, including the skin. We ecountered a unique case in which a 27-year-old Japanese man with WG presented with various typical cutaneous manifestations. Purpuric skin lesions and erythematous rash on the lower extremites progressively involved and changed into a necrotizing ulceration on his toe. Additionally, several nodules developed on the extensor surfaces of his elbows. His serum C-ANCA level increased remarkably. Leukocytoclastic vasculitis, the most common histopathological finding in WG patients, was detected in a purpuric lesion on his hand. A biopsy of a nodule on his elbow revealed palisading epithelioid histiocyte granulomas with features of lukocytoclastic vasculitis. The distinctive pattern of papules has been refferd to as „palisading neutrophilic granulomatous dermatitis". An open lung biopsy confirmed WG with focal necrotizing granuloma. A renal biopsy demonstrated necrotizng vasculitis and crescentic glomerulonephritis. He showed a good response to oral corticosteroids and cyclophosphamide with total remission of symptoms. We believe that a careful balance between the clinical manifestation and the histopathological evidence allows for timelly treatment of WG, which may prevent serious morbidity and death. Although uncommon, WG can clinicians should keep this diagnosis in mind when presented with these manifestation.

16. Pulmonary-renal syndrome

de Grootr K, Schnabel A

Internist (Berl) 2005 46 (7): 769-81.

Abstract Pulmonary-renal sndrome is a potentially life-threatening disorder, characterized by diffuse alveolar hemorrhage on the basis of pulmonary capillaritis in conjunction with rapidly progressive glomerulonephritis. Pulmonary-renal syndrome can originate from various systemic autoimmune disease. ANCA-associated account for approximately 60%, Goodpasture's syndrome for approximately 20% of the cases. Fulminant pulmonary capillaritis can result in acute respiratory failure, more subtle courses are only detected by broncoalveolar lavage. Renal biopsy displays extracapillary proliferating glomerulonephritis and renal immunhistology facilitates detection of the underlying systemic disease. By accelerating the diagnosis of the specific underlying disease, autoantibody testing fosters rapid initiation of treatment and thereby significantly improved the prognosis of pulmonary-renal syndrome. Intense immunosuppression with cyclophosphamide and glucocorticoids, augmented by plasmapheresis in the event of Goodpasture's syndrome, is the mainstay of therapy. Supportive measures as temporary ventilation and hemodialysis have further reduced mortality.

17. Autopsy case of microscopic polyangiitis with crescentic glomerulonephritis and necrotizing pancreatitis

Iwasa S, Katoh R

Pathol Int 2005 55 (8): 520-3.

Herein is reported the case of an 84-year-old woman who initially manifested rapidly progressive glomerulonephritis following a urinary tract infection. Laboratory findings showed a high titer of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA). Treatment with high-dose i.v. steroids resulted in clinical recovery and an undetectable MPO-ANCA titer. Two months later the patient was readmitted in a state of severe shock. Laboratory examination showed the deterioration of renal function, leucocytosis, and coagulation abnormalities consistent with disseminated intravascular coagulation (DIC). The patients died 12 days later. The post-mortem examination revealed necrotizing pancreatitis due to acute-stage vasculitis typified by fibrinoid necrosis of the arterioles and venules, and crescentic glomerulonephritis with healed-stage vasculitis. In the lungs, capillaritis with diffuse alveolar hemorrhage was not evident, but arteriolitis and phlebitis were occasionally seen. This case represents an unusual complication of necrotizing pancreatitis in the setting of microscopic polyangiitis. Thus, it is important to consider reactivation independent of the titer of ANCA in the course of the disease.

18. ANCA-negative pauci-immune renal vasculitis: histology and outcome

Eisenberger U, Fakhouri F, Vanhille P et al.

Nephrol Dial Transplant 2005 20: 1392-9.

Summary: See Part 2/PG/19

19. ANCA-negative pauci-immune crescentic glomerulonephritis complicated with recurrent massive gastrointestinal hemorrhage

Harad T, Uzu T, Namba T et al.

Clin Exp Nephrol 2005 9 (2): 174-8.

Abstract On April 25, 2003, a 62-year-old Japanese man had been admitted to a hospital because of heavy proteinuria and elevated serum creatinine level, and purpura on the lower extremities. On May 15, 2003, he was referred to our hospital for evaluation and treatment. Serum immunoglobulin and complements were within normal ranges. Immune serology was negative for antinuclear antibody, antiglomerular basement membrane antibody, and antineutrophil cytoplasmic antibodies. Histological examination of a percutaneous renal biopsy

specimen revealed that all of the glomeruli had severe creascent formation without deposits immunoreactants. A diagnosis of antineutrophil cytoplasmic antibody-negative pauci-immune crescentic glomerulonephritis was made. The patient was treated with one cycle of steroid pulse therapy (1000 mg methylprednisolone daily, given on 3 consecutive days), and subsequently with prednisolone (60 mg/day). Despite this treatment, renal failure progressed rapidly and hemodialysis was started 1 month after the acute presentation. On May 30, 2003, he sudden developed massive hematochezia. A technetium-targeted red-blood-cell scan suggested bleeding in the small intestine. On June 11, he presented with massive melena. A bleeding ulcer was found in third part of the dudenum, and was treated successfully with endoscopy, using a heater probe. On June 19, he presented with massive hematochezia again. Mesenteric angiopathy revealed active bleeding from the iliac branch of the superior mesenteric artery.He was treated with continous intraarterial vasopressin infusion by a catheter seated in the branch artery. The majority of patients with pauci-immune crescentic glomerulonephritis, one of the most common causes of rapidly progressive glomerulonephritis, have glomerular disease as part of a systemic vasculitis. Massive gastrointestinal bleeding, although rare, should be considered one of the serious complications in these patients.

20. Polyarteritis nodosa revisited

Colmegna I, Maldonado-Cocco JA

Curr Rheumatol Rep 2005 7 (4): 288-96.

Summary: See Part 2/ET/5

21. Altered activity of plasma hemopexin in patients with minimal change disease in relapse

Bakker WW, van Dael CM, Pierik LJ et al.

Pediatr Nephrol 2005 Aug 4 [Epub ahead of print]

Abstract Since an active isoform of plasma hemopexin (Hx) has been proposed to be a potential effector molecule in minimal change disease (MCD), we tested plasma and urine samples from subject with MCD in relapse (n=18) or in remission (n=23) (after treatment with prednisolone) for presence or activity of HX. For comparison, plasma or urine from proteiunuric subjects with focal and segmental glomerulosclerosis (FSGS n=11), membranoproliferative glomerulonephritis (MPGN n=9), IgA nephropathy (n=5) or healthy control donors (n=10), were incorporated into the study. Electrophoresis and Western blotting methods were used for evaluation of the Hx status, whereas protease activity of Hx was tested upon kidney tissue in vitro according to standard methods. The results show (1) a decreased mean titer of plasma Hx exclusively in MCD relapse subjects as compared with MCD in remission (0.21+/-0.14 mg/ml vs 0.44+/-0.06 mg/ml, $p<0.01$). mean HX titers in other proteinuric subjects ranged from 0.38+/-0.05 mg/ml to 0.40+/-0.06 mg/ml, whereas, the mean titer of healthy controls was 0.569+/-0.03 mg/ml Hx/ml; (2) an increased Hx activity /(expressed in arbitrary units) exclusively in plasma from MCD relapse subjects (3.3+/-0.72 vs 1,16+/-0.56, MCD remission; $p<0.01$);)3) different Western blot patterns in MCD relapse vs remission plasma; (4) reduced stainability or virtual absence of the 80-kD Hx band in blots of urine from MCD relapse in contrast to urine samples other proteinuric subjects with FSGS, MPGN, or IgA nephropathy. It is concluded that Hx in MCD relapse subjects may exist in an altered isoform, showing enhanced protease activity as compared with subjects in remission, subjects with other forms of primary glomerulopathy, or healthy control individuals.

22. C1q nephropathy with asymptomatic urine abnormalities

Nishida M, Kawakatsu H, Okumura Y et al.

Pediatr Nephrol 2005 Aug 16 [Epub ahead of print]

Abstract We found cases of C1q nephropathy (C1qN) among a total of 193 pediatric series of first renal biopsies. Among them, 94 biopsies were performed because of asymptomatic urine abnormalities detected by school urinary screening program in Japan; three cases out of these biopsies (3,2%) met the criteria of C1qN. One case out of them remaining 99 biopsies with symptomatic renal diseases (1%) also met the criteria of C1qN. Three cases with asymptomatic onset presenting with mild proteinuria with or without hematuria equally showed histologic features of membranoproliferative glomerulonephritis and showed improvements in urinanalysis without corticosteroid treatment. Our data suggest that membranoproliferative glomerulonephritis may be a common histological feature of asymptomatic pediatric C1qN in Japan and that this type of glomerulopathy may follow a relatively good course without steroid therapy.

23. Different glomerulopathies accompanying non-small-cell lung cancer

Paydas S, Soydas B, Paydas S et al.

Mt Sinai J Med 2005 72 (4): 279-81.

Summary: See Part 2/ET/10

24. Urinary Liver-Type Fatty Acid-Binding Protein: Discrimination between IgA Nephropathy and Thin Basement Membrane Nephropathy

Nakamura T, Sugaya T, Ebihara I et al.

Am J Nephrol 2005 25 (5): 447-50.

Abstarct Background: Microscopic hematuria without proteinuria is a common clinical finding in case of immunoglobulin A (IgA) nephropathy and thin basement membrane nephropathy. Liver-type fatty acid-binding protein (L-FABP) is expressed in renal proximal tubules and is reported to be a useful marker of the progression of chronic glomerulonephritis. Aim: To assess urinary FABP levels for differential diagnosis in patients with microscopic hematuria but without proteinuria. Methods: This was a multi-center retrospective study. Thirty adult patients who underwent renal biopsy for microscopic hematuria and 20 healthy adult volunteers were included in this study. Urinary L-FABP levels were measured by enzyme-linked immunosorbent assay and compared, particularly between those diagnosed with IgA nephropathy and those diagnosed with thin basement membrane nephropathy. Results: Twelve (40%) patients had IgA nephropathy, 6 (20%) had thin basement membrane nephropathy and 12 (40%) had normal biopsy findings. The urinary L-FABP level was significantly higher in patients with IgA nephropathy (38.4 +/- 26.8 mug/g Cr) than in healthy subjects (5.8 +/- 4.0 mug/g Cr) ($p < 0.01$); however, the level in patients with basement membrane nephropathy or normal biopsy results was comparable to that in healthy subjects. Follow-up data were available for of the 12 patients with IgA nephropathy who initially had no proteinuria. After 24 months, 4 of 11 were found to have proteinuria, and the urinary L-FABP level had increased from 40.6 +/- 30.5 mug/g Cr to 58.8 +/- 40.5 mug/g Cr ($p < 0.01$). Conclusion: Our data suggest that the urinary L-FABP level can be used to discriminate between IgA nephropathy and thin basement membrane nephropathy in patients with microscopic hematuria.

25. Urine protein patterns can serve as diagnostic tools in patients with IgA nephropathy

Haubitz M, Wittke S, Weissinger EM et al.

Kidney Int 2005 67 (6): 2313-20.

Abstract Background: IgA nephropathy (IgAN) is the most common chronic glomerular disease in adults. End-stage renal disease (ESRD) develops in about 30% of the patients. Early intervention and consequent therapy may prevent or at least delay the development of ESRD

in these patients. Up to now, the diagnosis could only the achieved with a renal biopsy. Methods: The urine of 45 patients with IgAN was collected and screened for protein/ploypeptide patterns with novel high throughput method, capillary electrophoreses on-line coupled to a mass spectrometer (CE-MS). CE-MS allows the fast and accurate evaluation of up to 2000 polypeptides in one urine sample. The results in IgAN were compared to findings in 13 patients with membranous nephropathy (MN) and 57 healthy individuals. Results: In the patiens with IgAN, even when urinary protein excretion was within the normal range of regular tests, the polypeptide pattern in urine differed significantly from that of healthy controls and patients with MN, indicating a specific „IgAN" pattern of polypeptide excretion. Classification regarding discrimination of IgAN from healthy controls and from MN had a sensitivity of 100% and 77%, respectively. Specificity was 90% and 100%, respectively. Compared to patterns estabilished earlier in patients with minimal change disease (MCD), focal segmental glomerulosclerosis (SGS), or diabetic nephropathy (DN), sensitivity and specificity were 100%. Treatment of the patients was associated with changes of the patterns, possibly indicating a therapeutic effect. Conclusion: Proteomic analysis with CE-MS coupling permits fast and accurate identification and differentiation of polypeptide patterns in the urine of patients with IgAN, allowing differentiation from healthy controls and, probably, other renal diseases.

26. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy

Honkanen T, Mustonen J, Kainulainen H et al.

Kidney Int 2005 67 (6): 2187-95.

Summary: See Part 2/PG/ 27

27. Diabetic nephropathy: common questions

Thorp ML

Am Fam Physician 2005 72 (1): 96-9.

Abstract Diabetic nephropathy, or diabetic kidney disease, affects 20 to 30 percent of patients with diabetes. It is common cause of kidney failure. Diabetic nephropathy presents in its erliest stage with low levels of albumin (microalbuminuria) in the urine. The most practical method of screening for microalbuminuria is to assess the albumin-to-creatinine ratio with a spot urine test. Results of two of three tests for microalbuminuria should more than 30 mg per day or 20 mcg per minute in a three- to six-month period to diagnose a patients with diabetic naphropathy. Slowing the progression of diabetic nephropathy can be achieved by optimizing blood pressure (130/80 mm Hg or less) and glycemic control, and by prescribing and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients with diabetes and isolated microalbuminuria or hypertension benefit from angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In the event that these mediactions cannot be prescribed, a nonhydropyridine calcium channel blockers may be considered. Serum creatinine and potassium levels should be monitored carefully for patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These medications should be stopped if hyperkalemia is pronounced.

28. Nephropathy, but not retinopathy, is associated with the development of heart disease in Type 1 diabetes: a 12-year observation study of 462 patients.

Torffvit O, Lovestam-Adrian M, Agardh E et al.

Diabet Med 2005 22 (6): 723-9.

Abstract Aim: To study the occurence of heart disease and death in Type 1 diabetic patients and evaluation whether presence of microangiopathy, i.e. nephropathy and retinopathy, was

associated with outcome. Methods: A 12-year observation study of 462 Type 1 diabetic patients without a previous history of heart disease at baseline who were treated under routine care in a hospital out-patient clinic. Results: A total of 85 patients developed signs of heart diasease, i.e. myocardial infarction (n = 41), angina n = 23), and heart failure (n = 17) and 56 patients died. The mortality for patients without signs of heart disease during the observation period was 7,6% compared with 51% in patients with myocardial infarction (P < 0.001), 26% in patients with angina (P < 0.01) and 65% in patients with heart failure (P < 0.001). The relative risk for death was 9.0 (P < 0.001) and 2.5 (P < 0.05) times higher in patients with macroalbuminuria and microalbuminuria, respectivelyy. The risk for cardiovascular death was 18.3 times (P < 0.001) higher in patients with macroalbuminuria compared with patients with normoalbuminuria. In patients with sight-threatening retinopathy, the relative risk for death was times higher (P < 0.01) and the risk for coronary heart disease events 4,4 higher (P < 0.05) compared with patients with no retinopathy. However, when retinopathy was adjusted for presence of macroalbuminuria, this association disappeared. Conclusion: This study shows a high incidence of heart disease in patients with Type 1 diabetes. The worse prognosis was seen in patients with sight-threatening retinopathy and macroalbuminuria and microalbuminuria at baseline. Macroalbuminuria and microalbuminuria were independently associated with a high risk for heart disease and death while the association with sight-threatening retinopathy only occured in the presence of nephropathy.

29. Insulin resistance and postprandial triglyceride levels in primary renal disease

Charlesworth JA Kriketos AD, Jones JE et al.

Metabolism 2005 54 (6): 821-8.

Abstract Background: Renal failure is associated with a range of metabolic abnormalities including insulin resistance and dyslipidemia. We examined the role of creatinine clearence (CrCl) and body composition in the development of insulin resistance in patients with primary renal disease and a variable degree of renal failure. We also determined the effect of a high-fat meal on postprandial triglyceride levels in a subgroup of these patients. Methods: Forty-four patients with primary renal disease (men, 25; women 19; age, 21-75 years) were compared to 44 controls matched for age, sex, and body composition. Renal biochemistry, plasma glucose, insulin, lipids, and nonesterified fatty acids were measured in the fasting state. Insulin sensitivity was calculated using the Homeostasis Model Assessment for Insulin resistance (HOMA-R), and pancreatic beta-cell secretory capacity by HOMA-beta. Fourteen normotriglyceridemic subjects from each group consumed an 80 g fat meal to examine their postprandial metabolic response. Results: Although there was no significant difference between HOMA-R for the controls and entire patients group (P = 0.06), HOMA-R was significantly higher in patients with CrCl less than 60 mL/min than those with CRCl greater than 6 mL/min or control subjects (P < 0.01 for each pair). Exponential analysis of the relationship between CrCl and HOMA-R and -beta showed a line of best fit that was superior to that obtained by linear regression analysisi (P < 0.01 and P < 0.005, respectively). HOMA-R in renal patients was correlated with several parameters of body composition, including central fat (kilogram) (P < 0.005). there was not difference in body fat parameters or HOMA-R for the patients and control subgroups undergoing a fat meal challenge. However, the patient subgroup showed a greater postprandial incremental rise in plasma triglycerides compared to controls (P < 0.02). Conclusion: Patients with renal disease exhibit metabolic features typically associated with the metabolic syndrome. Insulin resistance increased with decline in renal function and was significantly higher in patients with CrCl less than 60 mL/min compared to subjects with CrCL greater than 60 mL/min or carefully matched controls. Renal patients also showed significant postprandial hypertriglyceridemia.

30. Mechanical ventillation and acute renal failure

Kuiper JW, Groeneveld AB, Slutsky AS et al.

Crit Care Med 2005 33 (6): 1408—15.

Abstract Objective: To review the current literature on possible mechanisms by which mechanical ventillation may initiate or aggravate acute renal failure. Data Source: A Medline database and references from identified articles were used to perform a literature search relating to mechanical ventilation and acute renal failure. Data Synthesis: Acute renal failure may be initiated or aggravated by mechanical ventilation through three different mechanisms. First, strategies such as permissive hypercapnia or permissive may compromise renal blood flow. Second, through effects on cardiac output, mechanical ventilation affects systemic and renal hemodynamics. Third, mechanical ventilation may cause biotrauma pulmonary inflammatory reaction that may generate systemic release of inflammatory mediators. The harmful effects of mechanical ventilation my become more significant when a comorbidity is present. In these situations, it is more difficult to maintain normal gas exchange, and moderate arterial hypoxemia and hypercapnia are often accepted. Renal blood flow is compromised due to a decreased cardiac ouput as a consequence of high intrathoracic pressure. Furthermore, the effects of biotrauma are not limited to the lungs but may lead to a systemic inflammatory reaction. Conclusion: The development of acute renal failure during mechanical ventilation likely represents a multifactoral process that may become more important in the presence of comorbidities. Development of optimal interventional strategies requires an understanding of pathophysiologic principles and greater insight into the precise molecular and cellular mechanisms that also play a role.

V. TREATMENT

1. Apoptosis in glomerulonephritis

Hughes J, Savill JS

Curr Opin Nephrol Hypertens 2005 14 (4): 389-95.

Summary: See Part 2/PG/2

2. Angiotensin blockade in children with chronic glomerulonephritis and heavy proteinuria

Butani L

Pediatr Nephrol 2005 Aug 16 [Epub ahead of print]

Abstract Patients with chronic proteinuric nephropathies are at high risk of developing progressive renal insufficiency. There are limited controlled data on the efficacy of potentially toxic immunosuppressive therapies for many of these diseases such as immunoglobulin A nephropathy and idiopathic membranoproliferative glomerulonephritis. This limitation has not deterred healthcare providers from using such agents based on anecdotal experience. We report our experience taking care of three children with heavy proteinuria from chronic glomerular diseases. All were treated with combination of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers without concomitant immunosuppression. All went into complete remission soon after starting therapy, allowing corticosteroid avoidance. The purpose of this report is to make healthcare professionals more aware of the potential success that can be achieved with this relatively nontoxic drug regimen. Larger controlled clinical trials using this strategy are needed to better evaluate the efficacy and safety of this approach in children with glomerular disease.

3. Long-term follow-up atherosclerotic renovascular disease. Beneficial effect of ACE inhibition

Losito A, Errico R, Santirosi P et al.

Nephrol Dial Transplant 2005 20: 1604-9.

Summary: See Part 2/CP/2

4. Treatment with low-dose angiotensin-converting enzyme inhibitor (ACEI) plus angiotensin II receptor blocker (ARB) in pediatric patients with IgA nephropathy

Yang Y, Ohta K, Shimizu M et al.

Clin Nephrol 2005 64 (1): 35-40.

Abstract Aim: IgA nephropathy associated with heavy proteinuria is considered a more progressive form of this disease. In this report, we describe the favorable clinical effect of combination therapy with low doses of an angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) in the stage of pediatric IgA nephropathy associated with heavy proteinuria. Patients: We initially used ACEI for seven children with IgA nephropathy and heavy proteinuria who did not achieve remission with the routine treatment including steroids. Results: With ACEI therapy alone, only three patients showed an antiproteinuric response. In one of the three patients, the proteinuria decreased by half, but was still over 1 g/day. In the other four patients, the proteinuria did not decrease. In these

five patients, of whom one partial was a responder and four were non-responders for ACEI, ARB was added, and in marked contrast to ACEI therapy alone, the antiproteinuric effect was significantly augmented ($p<0.01$). The antiproteinuric response induced by combination was not accompanied by blood pressure changes. Urinary low-molecular protein and N-acetyl-ß-D-glucoseaminidase (NAG) levels tended to decrease after both ACEI alone and combination therapy. Conclusion: These data indicate that inhibition therapy of the angiotensin system not only decreases proteinuria levels but also protects renal tubular cells. Moreover, there were no obvious side effects associated with this therapy during follow-up period of our clinical trial. In conclusion, this report shows that the combination of low-dose of ACEI and ARB might provide marked antiproteinuric and long-term renoprotective effects in pediatric IgA nephropathy, with this approach appearing to be both well-tolerated and safe.

5. IgA: an immune glycoprotein

Yoo EM, Morrison SL

Clin Immunol 2005 116 (1): 3-10.

Summary: See Part 2/PG/23.

6. Aldolase reductase in diabetic microvascular complications

Chung SS, Chung SK

Curr Drug Targets 2005 6 (4): 475-86.

Summary: See Part 2/PG/29.

7. From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy

Wolf G, Chen S, Ziyadeh FN

Diabetes 2005 54 (6): 1626-34.

Summary: See Part 2/PG/31

8. Reduction of urinary connective tissue growth factor by Losartan in type 1 patients with diabetic nephropathy

Andersen S, van Nieuwenhoven FA, Tarnow L et al.

Kidney INT 2005 67 (6): 2325-9.

Abstract Background: Connective tissue growth factor (CTGF) is an important profibroticus cytokine implicated in development of diabetic glomerulosclerosis. Urinary CTGF is reported to be significantly increased in patients with diabetic nephropathy. The present study aimed to investigate the short- and long term effects of angiotensin II receptor blockade by Losartan on urinary CTGF levels in hypertensive type 1 diabetic patients with diabetic nephropathy. Methods: Seventy-one hypertensive type 1 diabetic patients with diabetic nephropathy were included in the study. After a washout period of 4 weeks, the patients received Losartan 50 mg, 100 mg, and 150 mg once daily in treatment periods each lasting 2 months. Thereafter, patients were followed prospectively during treatment with Losartan 100 mg o.d. with a total mean follow-up of 36 months. At baseline, after 2, 4, and 6 months then biannualy, urinary and plasma CTGF levels [enzyme linked immunosorbent assay (ELISA) fibrogen], albuminuria (Turbidimetry), glomerular filtration rate (GFR) [51-creatinineethylendiamintetraacetic acid (51)Cr-EDTA plasma clearence)] and 24 hours blood pressure (TM2420) were determined.

Results: Baseline levels of urinary and plasma CTGF were 7076 (5708 to 8770) ng/24 hours [geometric mean (95% CI)] and 12,7 (7,3) ng/mL [mean (SD)1, respectively. Albuminuria, GFR, and arterial blood pressure at baseline were 1152 (937 to 1416) mg/24 hours, 88 (24) mL/min1,73m(2), and 153/80 (17/9) mm Hg, respectively. Losartan significantly reduced urinary CTGF by 21% (9 to 31) (95% CI) totally (P < 0,05 vs. baseline); with no further reduction after increasing dose. The sustained reduction in urinary CTGF was 22% (12 to 32) (P < 0,05 vs. baseline). Rate of decline in GFR during the study was 3,2 (-1,6 to 15,9) mL/min/year [median (range)]. Redution in urinary CTGF was correlated with a lower rate of decline in GFR (r = 0,23, P = 0,05). Plasma CTGF remained unchanged throughout the study. Conclusion: Our 3-year study demonstrates that Losartan persistently reduces urinary CTGF excretion, which is associated with a slower rate of decline in GFR.

9. Pentoxifylline is as effective as captopril in the reduction of microalbuminuria in non-hypertensive type 2 diabetic patients - a randomized, equivalent trial

Rodriguez-Morán M, Guerrero-Romero F

Clin Nephrol 2005 64 (2) 91-7.
Abstract Aims: To compare the efficacy of pentoxifylline and captopril on urinary albumin excretion (UEA) rate in non-hypertensive diabetic patients with microalbuminuria. Methods: 450 subjects were screened; of these 130 eligible, non-hypertensive, type 2 diabetic subjects were enrolled and randomly allocated to receive either pentoxifylline 400mg t.i.d. (n = 65) or captopril 25 mg t.i.d. (n = 65) for six month in a randomized equivalent trial design study. Patients eligible to participate if they had microalbinuria, defined by UAE rate of 20-200 ug/min, and systolic/diastolic blood pressure lower than 140/85 mmHg. Diagnosis of high blood pressure and renal failure were exclusion criteria. In addition, subjects receiving ACE inhibitors or pentoxifyllin were not included. Results: Both treatments were well tolerated, without serious events; nonetheless, one subject (1,6%) in the group with pentoxifylline had severe headache, and three (4,7%) subjects in the group with captopril had intense dry cough and nasal congestion that required stopping pentoxifylline an captopril. In addition, slight headache and mild dry cough that did not require specific treatment or interruption of medication were present in two (3,2%) and five (7,8%) subjects treated with pentoxifylline and captopril. Four subjects dropped-out (one in the pentoxfylline group and three in the captopril group). Blood pressure and fasting glucose levels were similar between the two groups throughout the study. The UAE rate decreased from the first month of treatment in the subjects of both groups, a reduction that was sustained in the following months. At the end of the study, the average UAE rate in the subjects of both groups was lower than 25 ug/min. Conclusions: Pentoxifylline showed to be an effective alternative to ACE inhibitors in reducing UAE in non-hypertensive diabetic patients with microalbuminuria.

10. Increased tubular organic ion clearence following chronic ACE inhibition in patients with type 1 diabetes

Thomas MC, Jerums G, Tsalamandris C et al.

Kidney Int 2005 67 (6): 2494-9.

Abstract Background: The tubular excretion of creatinine significantly contributes to its clearence. Administration of an angiotensin-converting enzyme (ACE) inhibitor is associated with increased organic ion clearence in experimental diabetes. This study examines the effect and implications of chronic ACE inhibition on renal organic ion excretion in patients with type 1 diabetes. Methods: Samples were obtained from the Melbourne Diabetic Nephropathy Study Group (MDNSG) that randomized patients to receive perindopril (N= 11), nifedipine (N= 11), or placebo (N= 8). Albumin excretion rate, creatinine clearence, and isotopic glomerular filtration rate (GFR) were assessed at baseline and after 24 months. In addition, the clearence of the endogenous cations N-methylynicotinamide (NMN), creatinine, and the anion hippurate were determined by high-performance liquid chromatography (HPLC). Results: Following treatment with ACE inhibitor, perindopril, renal clearence of NMN was increased (+ 96%) (P < 0.05). There was no difference in patients treated with nifedipine (P= 0.25) and NMN

clearence fell in the placebo-treated patients (-26%) (P < 0.05). Changes in NMN clearence were unaffected after adjusting for the effects of perindopril on GFR. However, they were attenuated after adjusting for hippurate clearence, a marker of renal blood flow. This effect of perindopril on NMN clearence was seen in both men and women, regardless of baseline clearence and was correlated with reduced albuminuria following perindopril treatment. Conclusion: Organic ion clearence is increased in patients with diabetes following chronic ACE inhibition. This is consistent with experimental models showing increased ion transporter expression and improved tubular blood flow, following blockade of the renin-angiotensin system (RAS). These findings may have implications for the interpretation of creatinine-based indices in patients with diabetes.

11. Managing anaemia and diabetes: a future challenge for nephrologists

Eberhard R

Nephrol Dial Transplant 2005 20 [S6]: vi21-5.

Abstract The combination of diabetes and chronic kidney disease is associated with increased mortality and reduced quality of life. Recent studies have shown that, in general, late referral of patients to the renal unit increases mortality, and that patients with diabetes who are referred late have a particularly poor prognosis. Several co-morbid conditions have been shown to contribute to our patient outcomes, including both cardiovascular disease and anaemia. In patients with diabetic nephropathy, anaemia is more severe and is seen earlier than in patients with non-diabetic renal disease. Although the treatment of anaemia with recombinant human erythropoietin (rhEPO); epoetin) is well estabilished, the only data currently available concerning the effects of early intervention in patients with diabetic nephropathy are from small-scale studies. Therefore, two large-scale studies have been designed to provide information on the efficacy of epoetin treatment and on how current management stategies might be improved. The Anaemia CORrection in Diabetes (ACORD) study will provide information on the potential cardiac benefits of early anaemia management in patients with early, type 2 diabetic nephropathy. The Individualised Risk-profiling In Diabetes Mellitus (IRIDIEM) study will provide evidence-based guidance in risk factor management, by assessing the efficacy of individualized interventions.

12. IgG immunoabsorption reduces systemic lupus erythematosus activity and proteinuria: a long term observational study

Stumvoll GH, Aringer M, Smolen JS et al.

Ann Rheum Dis 2005 64 (7): 1015-21.

Abstract Objective: To analyse the effects of rigorous immunoglobulin removal by immunoabsorption (IAS) on proteinuria (primary outcome variable), disease activity (SIS, SLEDAI, ECLAM), and autoantibodies to double stranded DNA (anti-dsDNA) in active systemic lupus erythematosus (SLE). Methods: 16 patients with severe SLE and renal disease, in whom cyclophosphamide was contraindicated or failed to halt disease progression, were treated with IAS for 3 months. Patients acheiving at least 20% improvement in two or more of the outcome measures were considered responders and offered a 9 months' extension period. Results: Within 3 months, 14 patients responded and 11 opted for an extension. Proteinuria decreased from 6,7 (4,6) g/day (mean (SD)) at baseline to 4,3 (3,5) g/day at 3 moths and 2,9 (2,4 g/day at 12 months ($p<0,001$). From baseline to 3 and 12 months, disease activity improved independently of scoring by SIS (15 (5) to 5 (2) and to 5 (2), $p<0,0001$), SLEDAI (21 (7) to 5 (4) and to 5 (4), $p<0,0001$), or ECLAM (7 (2) to 2 (1) and to 3 (1), $p<0,0001$). Anti-dsDNA fell from 391 (647) IU/ml to 146 (248) and to 53 (50) IU/ml at 3 and 12 months, respectively. Steroids could be trapped from 117 (159) mg/day at baseline to 29 (17) mg/day at 3 months and 9 (2) mg/day at 12 months. IAS was not associated with an excess of infections. However, one patient died of septicemia after 1 month of treatment. Conclusion: In this negatively selected cohort of patients with SLE. IAS was associated with significant

response shown by reduced proteinuria, improved global disease activity, decreased anti-dsDNA, and lower glucocorticoid dosages, suggesting therapeutic benefit.

13. Successful treatment of progressive Henoch-Schonlein purpura nephritis with tonsilletomy and steroid pulse therapy

Sugiyama H, Watanabe N, Onoda T et al.

Intern Med 2005 44 (6): 611-5.

Abstract Henoch-Schonlein purpura (HSP) is a systemic disorders characterized by a leukocytoclastic vasculitis involving small vessels with the deposition of IgA immune complexes. The renal involvement is the major cause of morbidity and mortality in patients with HSP. We report here an adult patient with HSP nephritis (HSPN) accompained by persistent proteinuria and progressive renal dysfunction despite conventional therapy. The patients was successfully treated with tonsillectomy followed by intravenous pulse methylprednisolone and oral prednisone. The combination therapy resulted in a significant decrease in proteinuria, improvement of renal function and the disappearance of microhematuria. The patient finally reached a stage of clinical remission.

14. Pulmonary-renal syndome

de Groot K, Schnabel A

Internist (Berl) 2005 46 (7): 769-81.

Summary: See Part 2/CP/16

15. Rapidly-progressive glomerulonephritis in a patient with Behcet's disease: successful treatment with intravenous cyclophosphamide

Kim SD, Kim SH, Kim HR et al.

Rheumatol Int 2005 Jun 29 [Epub ahead of print]

Summary: See Part 2/ET/7

16. Failure of rituximab to treat a lupus flare-up with nephritis

Lambotte O, Durbach A, Kotb R et al.

Clin Nephrol 2005 64 (1): 73-7.

Abstract The autoantibodies secreted by B lymphoctes have recently been shown to play an important role in autoimmune disease. B lypmphocyte depletion by rituximab, a monoclonal antiCD20 antibody, has been introduced for the treatment of several autoimmune disorders. Few reports have underlined its potential use for the treatment of systemic lupus erythematosus (SLE). We report here the occurrence of extracapillary glomerulonephritis associated with a thrombotic event shortly after rituximab treatment for a lupus flare-up in a patients with anticardiolipin antibodies. This observation suggest that rituximab alone may be insufficient to control severe SLE with glomerulonephritis and should therefore be used with caution in patients with this conditions.

17. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab

Eriksson P

J Intern Med 2005 257 (6): 540-8.

Abstract Objectives: Rituximab (RIT) is a monoclonal anti-CD-20 antibody, wich depletes B-lymphocytes but not plasma cells. RIT is used for treatment of B-cell lymphomas, but has also shown beneficial effects in autoimmune diseases. In this case series RIT was used in anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. Design: Case series with a structured follow-up of treated patients. Setting: Departments of Nephrology and Rheumatology of an university hospital. Subjects: Two women with myeloperoxidase-ANCA-positive micrsocopic polyangiitis and seven patients (five men and two women) with proteinase 3-ANCA-posititve Wegener's granulomatosis. All patients were resistant to conventional therapy or had relapsed repeatedly after cessation of cyclophosphamide (Cyc). Interventions: The cases were treated with intravenous infusion of RIT once a week two times (three cases) or four times (six cases). To prevent fromation of antibodies to RIT, mycophenolate mofetil (five patients), azathioprine (one patient), or a short course of Cyc (two patients) were added or allowed to continue. Main Outcome Measures: Remission at 6 months assessed with Birmingham vasculitis activity score. The cases were followed 6-24 months and relapse rate was also noted. Results: Eight of nine patients responded completely and one case responded partially. Pulmonary X-ray improved (four cases), progress of lower extremity gangrene stopped (one case), remission of neuropathy was stable (one patient), renal vasculitis went into remission (two cases) and severe musculoskeletal pain improved (one case). Minor relapse in the nose occured in two cases. No adverse events or major infections were noted. Conclusion: RIT seems promising and safe in ANCA-positive vasculitis, and controlled studies should be conducted.

18. Mycophenolate mofetil – a new therapeutic agent for chronic autoimmune diseases

Harboe E, Goransson L, Wildhagen K et al.

Tidsskr Nor Laegeforen 2005 125 (12): 1650-2.

Abstract Background: Mycophenolate mofetil is an immunosuppressive agent frequently used in regimens to prevenet allograft rejection. In this review we focus on mycophenolate mofetil as a potential drug for chronic autoimmune diseases. Materials and Methods: We searched PubMed for relevant literature and present two case histories. Results and Interpretation: Treatment with mycophenolate mofetil is best documented in lupus nephritis. In this contaxt, some studies have documented an effect equal to cyclophosphamide for induction treatment, and equal to azathioprine, and better than cyclophosphamide for remission maintenance. Mycophenolate mofetil is today an alternative, although experimental, agent for the treatment of certain autoimmune diseases when conventional drugs have failed or are not tolerated; in the future it may become more widely used for immunosuppression. To estabilish the role for mycophenolate mofetil more prospective controlled studies are warranted.

19. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study

Mok CC, Tong KH, To CH et al.

Kidney Int 2005 68 (2): 813-7..

Abstarct Background: Tacrolimus is a relatively new calcineurin inhibitor that has been increasingly used in transplant medicine. The objective of the current work is to report our preliminary experience with tacrolimus in the treatment of diffuse proliferative glomerulonephritis in systemic lupus erythematosus (SLE). Methods: Nine consecutive patients who fulfilled the American College of Rheumatology criteria for SLE and biopsy-proven diffuse proliferative glomerulonephritis were recruited for an open-labeled trial with prednisolone and oral tacrolimus (0.1 mg/kg/day for 2 months, followed by 0.06 mg/kg/day). Prospective data on renal response and serologic lupus activity were collected. He efficacy

and safety of this regimen was reported. Results: Baseline characteristics of the patients were: mean age 33.3 +/- 12 years, women to men ratio 2:1, serum creatinine 94.2 +/- 46 micromol/L, daily proteinuria 4.56 +/- 2.4 g, seven (78%) patients were nephrotic, three (33%) were hypertensive, and four (44%) had elevated serum creatinine at the time of renal biopsy. At 6 months of therapy, complete and partial renal response was achieved in six (67%) and two (22%) patients, respectively. Significant improvement in proteinuria, hemoglobin, serum albumin, and C3 levels was observed in comparison with baseline values, starting at the second month. Tacrolimus was generally well tolerated, except for two patients who developed transient hyperglycemia. Infective complications, amenorrhea, hypertrichosis, gingivitis, new-onset hypertension, and significant increase in serum creatinine were not reported. Conclusion: Tacrolimus is an effective option for induction treatment of SLE-diffuse proliferative glomerulonephritis. Further trials are necessary to determine the optimal dosage and duration of therapy, and its efficacy in comparison to standard regimens.

20. Immunosuppressive therapy and clinical evolution in forty-nine patients with antineutrophil cytoplasmic antibody-associated glomerulonephritis

Kokolina E, Alexopoulos E, Dimitriadis C et al.

Ann N Y Acad Sci 2005 1051: 597-605.

Abstract Immunosuppressive therapy and clinical evolution were studied in 49 patients (29 females) with antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. The mean age of patients at presentation was 55 years, and the mean (+/-SD) follow-up was 43 months (+/-33) (range, 3-140). Among the 49 patients, 10 had biopsy.proven Wegener's granulomatosis, 33 microscopic polyangiitis, 2 Churg-Strauss syndrome, and 4 idiopathic crescentic glomerulonephritis. IgG ANCA autoantibodies were detected in all patients. Induction therapy included pulses and oral administration of methylprednisolone (MP) with oral administration of cyclophosphamide (CP) and plasma exchange in patients with alveolar hemorrhage and serum creatinine (SCr) levels >/= 6 mg/dL. CP was converted to azathioprine (AZA) or mycophenolate mofetil (MMF) after 3-6 months of therapy. Low doses of MP with or without AZA or MMF were administered until the end of follow-up. Therapy institution resulted in remission of disease in all patients. The mean SCr levels decreased from 4.9 mg/dL (+/-2.5) at the onset of the disease to 2.8 mg/dL (+/-1.7) (P < 0.0001), and 3.2 mg d/L (+/-2.3) (P < 0.0001) after 3 and 6 months, respectively. At the end of follow-up, 17 (35%) patients progressed to end-stage renal disease after 34 months (+/-29) (range, 3-98), and 30 (61%) patients maintained sufficient renal function. Two patients deaths were attributed to immunosuppression. Patients with high SCr levels at diagnosis and severe interstitial fibrosis found in renal biopsy had poor renal outcome ((P < 0.01 and P < 0.02, respectively). Induction therapy with MP and CP seems to be the regimen of choice in patients with ANCA-associated glomerulonephritis. Early diagnosis and therapy institution as well as long-term trearment lead to acceptable renal survival.

21. Treatment with cytapheresis for antineutrophil cytoplasmic antibody-associated renal vasculitis and its effect on anti-inflammatory factors.

Hasegawa M, Watanabe A, Takahashi H et al.

Ther Apher Dial 2005 9 (4): 297-302.

Abstract To evaluate the efficacy of cytapheresis for the treatment of rapidly progressive glomerulonephritis (RPGN) caused by myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis, the renal prognosis and the mortality rate at 1 year after treatment were compared between a Cytapheresis Group and a Steroid Pulse Group. The Cytapheresis Group included 10 patients who were treated with cytapheresis and oral corticosteroids. Five had granulocytapheresis with the Adacolumn (Japan Immuno Research Laboratories Co. Ltd, Takasaki, Japan) and the remaining five had leukocytapheresis with the leukocyte removal filter, Cellsorba (Asahi Medical Co. LTd, Tokyo Japan). The Steroid Pulse Group was comprised of 12 patients who were treated with methylprednisolone pulse therapy

and oral corticosteroids. In the Cytapheresis Group, renal function recovered in 70% of the patients and the mortality rate was 10%. In the Steroid Pulse Group, renal function recovered in 66.7% and the mortality rate was 33.3%, with infection as the cause of death. Total doses of corticosteroids converted to prednisolone dose during a 1 month period, ranged from 280 mg to 1226 mg in the Cytapheresis Group. On the other hand, these dosage ranged from 2376 mg to 8380 mg in the Steroid Pulse Group. These results indicated that the mortality rate by infection could be reduced by adding cytapheresis therapy. Concerning the mechanism of cytapheresis, anti-inflammatory factors such as soluble tumor necrosis factor receptor, and interleukin-10 reduced after cytapheresis. These changes might be responsible for efficacy of cytapheresis. In conclusion, cytapheresis is thought to be one of effective treatments for RPGN caused by MPO-ANCA-associated vasculitis, reducing the levels of anti-inflammatory factors.

22. Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome

Mendizabal S, Zamora I, Berbel O et al.

Pediatr Nephrol 2005 20 (7): 914-9.

Abstract Attempts to minimize the effects of prolonged steroid use in steroid-dependent nephrotic syndrome (SDNS) and the need to overcome steroid resistance (SRNS) justifies immunosuppressant therapy. We report our experience in a cohort of patients with SD/SRNS during the administration of mycophenolate mofetil (MMF) in a prospective protocol initiated in January 2001. Twenty-six children with idiopathic nephrotic syndrome were included (21 steroid dependent and 5 steroid resistant), whose response did not change after sequential treatment with cyclophosphamide (CPM) and cyclosporine (CsA). Histopathologic patterns were: 11 minimal change disease (MCD), 1 diffuse mesangial proliferation (DMP), 13 focal segmental glomerulosclerosis (FSGS) and membranous 1 glomerulonephritis (MGN). The median age of onset of NS was 2.8 years (range 1.2-12.5), and treatment with MMF was performed at a median age of 11.4 years (range 5-17) with an initial dose of 600 mg/m(2)/12 h, adjusted to maintain levels of mycohenolate acid (MPA) at 2.5-5 mcg/ml. The planned duration of study to assess treatment efficacy was 6 months. The mean MMF dose required was 624 (SD=136) mg/m(2)/12 h (range 415-970), which maintained mean C(0)-MPA levels of 2.9 (SD=1.71) mcg/ml (range 1.2-5.9 mcg/ml). In the five patients with SRNS, only one achieved complete remission. In the patients with SDNS, steroid sparing was achieved in 15 and 9 remained in remission on MMF monotherapy. Withdrawal of MMF resulted in immediate relapse in 47%. In our study, MMF was a useful immunosuppressant due to its fewer undesirable effects and similar efficacy to other drugs used. It appears effective for the maintance of remission in SDNS patients, with a response similar that of CsA.

23. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

Frisch G, Lin J, Rosenstock J et al.

Nephrol Dial Transplant 2005 2005 Jul 19 [Epub ahead of print]

Abstract Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. Up to 40% progress to end-stage renal disease (ESRD) over 10-20 years. Currently, treatment is limited. We studied the use of mycophenolate mofetil vas placebo in a group of North American IgAN patients at high risk for progressive disease. Methods: Included were 32 patients aged 18-75 years from multiple centres who had their biopsies read at Colimbia and who had at least 1 g of proteinuria per day plus at least two of the following risk factors: (i) male sex; (ii) hypertension >150/90 mmHg or requring antihypertensive medications; (iii) creatinine clearence, measured by 24 h urine collection, <80 and >20 ml/min at time of enrolment; and (iv) presence of glomerulosclerosis or tubulointerstitial atrophy and fibrosis on renal biopsy. Patients were randomized to either 1 year of MMF, titrated up to a dose of 1000mg bid, or placebo. Total follow-up was 2 years. All patients received angiotensin inhibition medication. The primary outcome was a 50%

increase in baseline serum creatinine (SCr). Secondary outcomes were an increase of 0.5 mg/dl SCr, ESRD and a 50% reduction in proteinuria. Results: The mean baseline SCr was 2.4 mg/dl. No statistically significant differences were observed for any outcome. Five of 17 who received MMF vs two of 15 in the placebo group reached a 50% increase in SCr (P = 0.4). In both groups, all patients who reached the primary outcome also reached ESRD. Ten who received MMF vs seven who received placebo had a 0.5 mg/dl increase in SCr (P = 0.7). Only three MMF and two placebo patients had a 50% reduction in 24 proteinuria. No serious adverse events occured in either group. Conclusion: No benefit was seen in patients who received MMF in this high risk group, probably reflecting the relatively advanced stage of disease of our population. We conclude that MMF is probaly not effective in pateinst with IgAN who already have moderate renal insufficiency.

24. Glomerulonephritis due to antineutrophil cytoplasm antibody-associated vasculitis: An update on approaches to management

Little MA, Pusey CD

Nephrology (Carlton) 2005 10 (4): 368-76.

Summary: See Part 2/CP/14.

25. Etanercept plus Standard Therapy for Wegener's granulomatosis

The Wegener's Granulomatosis Etanercept Tial (WGET) Research Group

N Engl J Med 2005 352: 351-61.

Abstract Background: The majority of patients with wegener1s granulomatosis have disease flares after conventional medications are trapered. There is no consistently safe, effective treatment for the maintanence of remission. Methods: We conducted a randomized, placebo-controlled trial at eight centers to evaluate etanercept for the maintenance of remission in 180 patients with Wegener's granulomatosis. The primary outcome was sustained remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis of 0 for at least six months (score can range from 0 to 67, with higher scores indicating more active disease). In addition to etanercept or placebo, patients received standard therapy (glycocorticoids plus cyclophosphamide or methotrexate). After remission, standard medications were tapered according the protocol. Results: The mean follow-up for the overall cohort was 27 onths. Of the 174 patients who could be evaluated, 126 (72.4 percent) had a sustained remission, but only 86 (49.4 percent) remained in remission for the remainder of the trial. There were no significant differences between the etanercept and control groups in the rates of sustained remission (69.7 percent vs. 75.3 percent, P=0.39), sustained periods of low-level disease activity (86.5 percent vs. 90.6 percent, P=0.32), or the time required achive those measures. Disease flares were common in both groups, with 118 flares in the etanercept group (23 svere and 95 limited) and 134 in the control group (25 severe and 109 limited). There was no significant difference between the etanercept and control groups in the relative risk of disease flares per 100 person-years of folow-up (0.89, P=0.54). During the study, 56.2 percent of patients in the etanercept group and 57.1 percent of those in the control group had at least one severe of life-threatening adverse event or died (P=0.90). Solid cancers developed in six patients in the etanercept group, as compared with none in the control group (P=0.01). Conclusions: Etanercept is not effective for the maintenance of remission in patients with Wegener's granulomatosis. Durable remission were achieved in only a minority of the patients, and there was a high rate of treatment-related complications.

26. Aggravation of anti-myeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumor-necrosis factor-alpha

Huugen D, Xiao H, van Esch A et al.

Am J Pathol 2005 167 (1): 47-58.

Abstract Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and idiopathic pauci-immune necrotizing crescentic glomerulonephritis are associated with myeloperoxidase (MPO)-specific anti-neutrophil cytoplasmic autoantibodies (ANCAs). Clinical and experimental evidence indicates that ANCA and proinflammatory stimuli of infectious origin act synergistically to cause vasculitis. We tested this hypothesis in a recently developed mouse model of anti-MPO IgG-induced glomerulonephritis by using bacterial lipopolysaccharide (LPS) as the pronflammatory stimulus. Systemic administration of LPS dose dependently increased renal injury induced by anti-MPO IgG as demonstrated by increased glomerular crescent formation and glomerular necrosis. In the early phase, LPS enhanced anti-MPO IgG glomerular neutrophil accumulation. Furthermore, a transient induction of circulating tumor necrosis factor (TNF)-alpha levels, followed by a marked increase in circulating MPO levels, was observed on administration of LPS. In vitro, anti-MPO IgG induced a respiratory burst in murine neutrophils only after priming with TNF-alpha. Finally, anti-TNF-alpha treatment attenuated, but did not prevent, the LPS-mediated aggravation of anti-MPO IgG-induced glomerulonephritis. In conclusion, our study demonstrates that ANCA and proinflammatory stimuli act synergistically to induce vasculitis disease and suggests potential benefits of inhibiting TNF-alpha bioactivity in treating human ANCA-associated necrotizing crescentic glomerulonephritis.

27. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET)

Seo P, Min YI, Holbrook JT et al.

Arthritis Rheum 2005 52 (7): 2168-78.

Abstract Objective: To analyze damage occuring in patients with Wegener's granulomatosis (WG) enrolled in the WG Etanercept Trial (WGET) and to correlate that damage with disease activity, adverse events, and quality of life. Methods: The Vasculitis Damade Index (VDI) was applied to all 180 patients at trial entry and every 6 months throghout the trial. Items of damage were analyzed by presumed etiology (i.e., secondary to WG, to therapy, or both) and time of occurence. Spearman's rank correlation coefficients were calculated between VDI scores and the Birmingham Vasculitis Activity Score for WG (BVAS/WG), frequency of flares, number of adverse events, and the patients' quality-of-life assessments. Results: The mean VDI score was 1.3 at the study enrollment and 1.8 at the end of the trial. This increase was due to damage that occured despite (or because of) therapy, including visual impairment, hearing loss, nasal blockade, pulmonary fibrosis, hypertension, renal insufficiency, peripheral neuropathy, gonadal failure, and diabetes mellitus. Only 11% of the enrolled patients had not sustained a single VDI item after 1 year enrollment. When adjusted for baseline VDI, the baseline BVAS/WG correlated moderately well with the VDI score at 1 year ($r = 0.20$, $P = 0.015$). Increases in adjusted VDI scores also correlated with the number of adverse events, particularly among patients with limited WG ($P = 0.06$). Conclusion: Damage from both active disease and its treatment remain important problems for patients with WG. Despite the dramatic improvements in patients survival achieved over the last several decades, only a few patients with WG emerge from a period or active disease without sustaining some damage from the disease itself, its treatment, or both. An important measure of future therapeutic approaches will be ability to reduce the damage accrued over time.

28. Low frequency of renal function impairment during one-year of therapy with tenofovir-containing regimens in the real-word: a case-control study

Padilla S, Gutierrez F, Masia M et al.

AIDS Patient Care STDS 2005 19 (7): 421-4.

Abstract Concern exist about the risk of nephrotoxicity using tenofovir (TDF) in HIV-infected patients. We performed a retrospective case-control study including 122 consecutive TDF-

naive patients who started treatment with TDF-containing regimes and 194 patients receiving antiretroviral therapy with other antiretroviral drugs. During a 12-month observation period 5 (4.1%) patients in the TDF group versus 1 (0.5%) in the control group developed grade 1 or higher serum creatinine elevations (p = 0.018). Only 2 (1.6%) patients discontiunued TDF treatment as a result of serum creatinine elevations. In 4 of 5 patients developing creatinine elevations TDF was combined with lopinavir-ritonavir. The use of TDF in clinical practice during a 12-month period is associated with low risk of mild renal failure. Further studies to assess long-term renal safety of this drug are needed.

29. Polyarteritis nodosa revisited

Colmegna I, Maldonado-Cocco JA

Curr Rheumatol Rep 2005 7 (4): 288-96.

Summary: See Part 2/ET/5.

30. Cardiovascular risk factors in severe chronic renal failure: the role of dietary treatment

Bergesio F, Monzani G, Guasparini A et al.

Clin Nephrol 2005 64 (2): 103-12.

Abstract Background: Lipoprotein abnormalities and increased oxidized LDL (OxLDL) are often observed in uremia and are reported to play a centrale role in the development of cardiovascular disease (CVD). Vegan diet, known fot its better lipoprotein profile and anioxidant vitamin content, could protect against CVD. Aim of this study was to investigate the influence of vegan diet supplemented with essential amino acids (EAA) and ketoanalogues (VSD) on both traditional and non-traditional cardiovascular risk factors (CVRF). Methods: Twenty-nine patients (18 M, 11 F) aged 35 years (range 29-79 years) with advanced chronic renal failure (median sCr: 5.6 mg/dl) on very low protein vegetarian diet (0.3g/kg/day) supplemented with a mixture of EAA and ketoacids (VSD) and 31 patients (20 M, 11 F) aged 65 years (range 29-82 years) on conventional low-protein diet (CD: 0.6 g/kg/day) with a similar renal function (median sCr: 5.2 md/dl), were investigated for lipids and apolipoprotein parameters (traditional CVRF) as well as for oxidative stress (oxidized LDL, antibodies against OxLDL and thiobarbituric acid-reactive substances (TBARS), total homocysteine (tHCY), liporotein(a) (lp(a)), albumin and c-reactive protein (CRP) (non-traditional CVRF) including vitamins A, E, B12 and folic acid. Results: Compared to patients onn CD those on VSD sshowed increased HDL-cholesterol levels ($p<0.005$) with a reduction of LDL cholesterol ($p<0.01$) and an increase of apoA/apoB ratio ($p<0.02$). Among non-traditional CVRF, a mild but significant reduction of OxLDL ($p<0.05$) with lower TBARS concentrations ($p<0.01$) and a significant reduction of total homocysteine ($p<0.002$), Lp(a) ($p<0.002$) and CRP levels ($p<0.05$) were also observed in these patients. Concentrations of vitamin E and A not different between tweo groups while vitamin B12 and folic acid resulted markedly increased in patients on VSD. OxLDL significantly correlated with total and LDL cholesterol, triglycerides and ApoB in CD but not in VSD patients. Patients on CD also showed a significant correlation between urea and CRP. After multivariate analysis, only urea ($p<0.001$) and OxLDL ($p<0.006$) were associated to a risk of CRP > 0.3 mg/dl. Conclusions: These results indicate a better lipoprotein profile in patients on vegan diet including non-traditional CVRF. In particular, these patients show a reduced oxidative stress with a reduced acute-phase response (CRP) as compared to patients on conventional diet. We hypothesize that urea, significantly lower in patients on VSD, may account, possibly together with the reduction of other protein breakdown products, for the decreased acute.phase response observed in these patients. Our findings suggest that low-protein diets, and vegan in particular, may exert a beneficial effect on the development of cardiovascular disease in patients with end-stage renal disease (ESRD).

31. Effect of alcohol consumption on estimated glomerular filtration rate and creatinine clearence rate

Chung FM, Yang YH, Shieh TY et al.

Nephrol Dial Transplant 2005 20: 1610-6.

Abstract Background: Moderate alcohol consumption is widely recognized as beneficial in the prevention of cardiovascular disease, yet the renal effects of alcohol intake are still controversial. The present study is designed to investigate the influence of alcohol consumption on calculated creatinine clearence rate (CCr) and glomerular filtration rate (GFR) in a Southern Taiwan Pai-Wan aboriginal community with a high prevalence of alcohol consumption. Methods: This is a cross-sectional community-based study. The 1466 aboriginal subjects, 40-95 years of age, are a stratified random subpopulation identified during an integrative health care programme. They were sampled for drinking patterns. The main outcome measurements were serum creatinine, estimated CCr and GFR. Results: Subjects with alcohol consumption had significantly higher levels of serum triglycerides, high-density lipoprotein cholesterol, uric acid, estimated CCr and GFR values than non-drinkers. Their blood pressure was also significantly higher. They had lower total cholesterol and low-density lipoprotein cholesterol concentrations. Increasing alcohol consumption was independently and significantly associated with a higher level estimated CCr and GFR when analysed as both a categorical and continous variable. Conclusions: The present study shows that chronic alcohol consumption has a negative effect on blood pressure and lipid profile and stimulates the estimated GFR.

32. Longitudinal follow-up of bone mineral densitiy in children with nephrotic syndrome and the role of calcium and vitamin D supplements

Gulati S, Sharma RK, Gulati K et al.

Nephrol Dial Transplant 2005 20: 1598-1603.

Abstract Background: We previously have demonstrated that children with idiopathic nephrotic syndrome (INS) are risk of metabolic bone disease (MBD). In this study, we report the longitudinal follow-up of these children and the role of calcium and vitamin D supplements. Methods: We prospectively studied 100 consecutive children with INS. They were treated with prednisone. All were subjected to a baseline clinical, biochemical and radiological evaluation. They were initiated on calcium (500mg/day) and vitamin D3 (200IU/day) supplements, followed by a repeat assessment. The primary outcome measure was the ^_z score (difference between the initial and final z scores) on dual energy X-linked absorptiometry (DEXA). A univariate and multivariate analysis using stepwise linear regression was performed for factors predictive of an improved ^_z score. Results: Of the 88 children that completed the study, the majority (n=54) had improved bone mineral density (BMD) at the spine, and another 25 children had stable BMD on calcium and vitamin D3 supplements. The mean spinal BMD values were significantly better on follow-up (0.607+_0.013g/cm(2)) as compared with baseline values (0.561+_0.010g/cm(2)). (P<0.0001). The interval between initial and follow-up assessment was 1.5+_0.07 years. Children who were on these supplements (n=73) had a significantly improved z score as compared with those who did not receive them (n=15) (P=0.0008). On multivariate analysis, the factors predictive of an improved z score were: younger age (P<0.0001), calcium and vitamin D3 supplemet (P<0.0001), greater dietary calcium intake (P=0.022) and lower interval steroid dose (P=0.001). Conclusions: Children with greater steroid doses were likely to have low BMD on follow-up. Calcium and vitamin D supplements may help in improving BMD in children with INS.

33. Roscovitine targets, protein kinases and pyridoxal kinase

Bach S, Knockaert M, Reinhardt J et al.

J Biol Chem 2005 280 (35): 31208-19.

Abstract (R)-Roscovitine (CYC202) is often referred to as a „selective inhibitor of cyclin-dependent kinase". Besides its use as a biological tool in cell cycle, neuronal functions, and apoptosis studies, it is currently evaluated as a potential drug to treat cancers, neurodegenerative diseases, viral infections, and glomerulonephritis. We have investigated the selectivty of (R)-roscovitine using three different methods: 1) testing on a wide panel of purified kinases that, along with previously published data, now reaches 151 kinases; 2) identifying roscovitine-binding proteins from various tissue and cell types following their affinity chromatography purification on immobilized roscovitine; 3) investigating the effects of roscovitine on cells deprived of one of its targets, CDK2. Altogether, the results show that (R)-roscovitine is rather selective for CDKs, in fact most kinases are not affected. However, it binds an unexpected, non-protein kinase target, pyridoxal kinase, the enzyme responsible for phosphorylation and activation of vitamin B(6). These results could help in interpreting the cellular actions of (R)-roscovitine but also in guiding the synthesis of more selective roscovitine analogs.

34. Comparison of continous and intermittent renal replacement therapy for acute renal failure

Uehlinger DE, Jakob SM, Ferrari P et al.

Nephrol Dial Transplant 205 20: 1630-7.

Abstract Background: Mortality rates of critically ill patients with acute renal failure (ARF) requiring renal replacement therapy (RRT) are high. Intermittent and continous RRT are available for these patients on the intensive care units (ICUs). It is unknown which technique is superior with respect to patients outcome. Methods: We randomized 125 patients to treatment with either continous venovenous haemodiafiltration (CVVHDF) or intermittent haemodialysis (IHD) from a total of 191 patients with ARF in a tertiary-care university hospital ICU. The primary end-point was ICU and in-hospital mortality, while recovery of renal function and hospital lenght of stay were secondary end-points. Results: During 30 months, no patient escaped randomization for medical reasons. Sixty-six patients were not randomized for non-medical reasons. Of the 125 randomized patients, 70 were treated with CVVHDF and 55 with IHD. The two groups were comparable at the start of RRT with respect to age (62±15 vs 62±15 years, CVVHDF vs IHD), gender (66 vs 73% male sex), number of failed organ systems (2.4±1.5 vs 2.5±1.6). Simplified Acute Physiology Scores (57±217 vs 58±23), septicaemia (43 vs 51%), shock (59 vs 58%) or previous surgery (53 vs 45%). Mortality rates in the hospital (47 vs 51%), CVVHDF vs IHD, P=0.72) or in the ICU (34 vs 38%, P=0.71) were indpendent of the technique of RRT applied. Hospital lenght of stay in the survivors was comparable in patients on CVVHDF [median (range) 20 (6-71) days, n=36] and in those IHD [30 (2-89) days, n=27, P=0.25]. The duration of RRT required was tha same in both groups. Conclusion: The present investigation provides no evidence for a survival benefit of continous vs intermittent RRT in ICU patients with ARF.

35. Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study

Fiaccadori E, Maggiore U, Rotelli C et al.

Nephrol Dial Transplant 2005 20: 1976-80.

Abstract Background: Thus far, there have been no controlled studies to examine optimal of energy provision in critically ill patients with acute renal failure (ARF) receiving artifical nutrition. Methods: After a 24h nitrogen-free regimen (20% dextrose), we assigned during an open-label AB/BA-crossover-trial, 10 ARF patients receiving both total parenteral nutrition (TPN) and reanl replacement therapy (seven males; mean age 72 years, range 60-83; mean APACH II score 27.1 range 23-24, mechanical ventillation 8/10 to a lower caloric-TPN regimen (30kcal/kg/day) and to a higher calorie-TPN regimen (40kcal/kg/day), each for 3

days. Nitrogen intake was 0.25g/kg/day for both regimens. We estimated nitrogen balance, protein catabolic rate and urea generation rate by urea kinetic methods based on both timed blood samples of serum urea and direct urea quantification from dialysis fluid. Results: Two patients were excluded from the analysis (due to death and serum triglycerides above 5,1 mmol/l, respectively). Compared with lower caloric-TPN, the higher caloricTPN regimen did not improve estimated nitrogen balance [+1.55g/day (95% confidence interval: -0.95 to +4.05, P=0.18)], protein catabolic rate [-0.10g/kg/day (-0.33 to +0.14, P=0.35)], or urea generation rate [-1.3mg/min (-5.2 to +2.7, P=0.46)], whereas it increased serum triglycerides [+1.36mmol/l (+0.53 to +2.19, P=0.007)], glucose [+1.15mmol/l (+0.07 to +2.24, P=0.0041)], insulin need [+20.4 U/day (+8.3 to +32.6, P=0.006)] and nutritional fluid administration [+468ml/day (+370 to +566, P<0.001)]. Conclusion: The present study, conducted in a small group of subjects, shows that in critically ill patients with ARF on a nitrogen intake of 0.25g/kg/day, an energy provision of 40kcal/kg/day does not improve nitrogen balance estimates compared with a 30kcal/kg/day intake, instead, it may increase the risk of artificial nutrition-related side-effects.

36. Contrast media-induced nephropathy: clinical burden and current attempts for prevention

Habeb M, Agac MT, Aliyev F et al.

Anadolu Kardiyol Derg 2005 5 (2): 124-9.

Abstract Contrast media-induced nephropathy is the third most common cause of hospital acquired acute renal failure. With increasing use of contrast media in diagnostic and interventional procedures it has become one of the major challenges encountered during routine cardiology practice. Despite clinical importance it is an under-recognized event with major morbidity and mortality. Risk of developing contrast media-induced nephropathy depends mainly on patients preexisting characteristics and physicochemical properties of the contrast agent. Primary attempts for the prevention of contrast mediainduced nephropathy should include systemic review of patient's characteristics and risk stratification. Patients at the greatest risk for contrast media-induced nephropathy can be definied as those having preexisting impaired renal function, diabetes mellitus, and congestive heart failure. Other risk factors include: age above seventy years, female gender, dehydration and use of high volume contrast media. The more expeditious use of iso-osmolar non-ionic contrast media reduced the incidence of contrast media related renal dysfunction. Currently, the only widely proven method of reducing the risk of contrast media-induced nephropathy is adequate pre- and postprocedural hydration. In addition, prophylactic use of free radical scavenger N-acetylcysteine has been swon to prevent contrast media-induced nephropathy in some moderate-scale clinical trials and a meta-analysis. Despite the attempts to reduce the risk of contrast nephropathy, this clinical event affects over 25% of high risk patients and mortality remains to be high.

37. Theophylline for prevention of contrast-induced nephropathy - A systematic review and meta-analysis

Bagshaw SM, Ghali WA

Arch Intern Med 2005 165: 1087-93.

Abstract Background: Contrast-induced nephropathy (CIN) is an important cause of declines in kidney function and is related to greater morbidity, health care costs, and mortality. Adenosine has been proposed to contribute to the pathophysiological process of CIN. We performed a systematic review and meta-analysis of theophylline, an adenosine antagonist, for the prevention of CIN. Data Sources: Studies were identified in all languages by search of MEDLINE (1966 through November 2003), EMBASE (1980 through week 44 [November] of 2003), and the Cochrane Clinical Trials Register (1996 through November 2003) databases and selected conference proceedings. Study Selection: We searched for randomized controlled trials comparing theophylline vs control in patients receiving radiocontrast media for angiography or computed tomography. Data Extraction: Our primary outcome measures were

the risk of CIN, the difference in serum creatinine levels between theophylline and control groups at 48 hours and need for dialysis. Data Synthesis: Nine randomized controlled trials involving 585 patients were identified and included for analysis. Theophylline protocols and definitions of CIN varied across studies. There was evidence of heterogeneity of results across trials (Q=9.77; P = 0.08); therefore, pooled odds ratio (OR) using a conservative random-effects model was 0.40 (95% confidence interval [CI], 0.14 to 1.16; P = 0.09) indicating trend toward reduction in the incidence of CIN with teophylline use. The pooled estimate for the difference in 48-hour serum creatinine levels between the theophyllin and control groups was -0.17 mg/dL [95% CI, -24.6 to -5.7 umol/L]) (P = 0.002), indicating that theophylline may be protective in CIN. The incidence of CIN requring dialysis was uncommon and reported in only 1 case. Conclusions: Theophylline may reduce the incidence of CIN with an efficacy that is perhaps comparable to that reported in studies of N-acetylcysteine. However, findings are inconsistent across studies. A large, well-designed trial that incorporates the evaluation of clinically relevant outcomes is requred to more adequately assess the role for theophylline in CIN prevention.

38. Perioperative N-acetylcysteine to prevent renal dysfunction in high-risk patients undergoing CABG surgery: a randomized controlled trial

Burns KE, Chu MW, Novick RJ et al.

JAMA 2005 294 (3): 342-50.

Abstract Context: Renal dysfunction is a complication of coronary artery bypass graft (CABG) surgery performed with a cardiopulmonary bypass (CPB) that is associated with increased morbidity and mortality. N-acetylcysteine, an antioxidant and vasidilator, counteracts renal ischemia and hypoxia. Objective: To determine whether perioperative intravenous (IV) N-acetylcysteine preserves renal function in high-risk patients undergoing CABG surgery with CPB compared with placebo. Design, Setting, and Patients: Randomized, quadruple blind. Placebo-controlled trial (October 2003 - September 2004) in operating rooms and general intensive care units (ICUs) of 2 Ontario tertiary care centers. The 295 patients required elective or urgent CABG and had at least 1 of the following: preexisting renal dysfunction, at least 70 years old, diabetes mellitus, impaired left ventricular function, or undergoing concomitant valve or redo surgery. Interventions: Patients received 4 (2 intraoperative and 2 postoperative) doses of IV N-acetylcysteine (600mg) (n = 148) or placebo (n = 147) over 24 hours. Main Outcomes Measures: The primary outcome was the proportion of patients developing postoperative renal dysfunction, defined by an increase in serum creatinine level greater than 0.5 mg/dL (44 micromol/L) or a 25% increase from baseline within the first 5 postoperative days. Secondary outcomes included postoperative interventions and complications, the requirement for renal replacement therapy (RRT), adverse events, hospital mortality, and ICU and hospital lenght of stay. Results: There was no differences in the proportion of patients with postoperative renal dysfunction (29.7% vs 29.0%, P = 0.89, relative risk (RR), 1.03 [95% confidencia interval {CI}, 0.72-1.46]) in the N-acetylcysteine and placebo groups, respectively. We noted nonsignificant differences in postoperative interventions and complications, the need for RRT (0.78% vs 2.18%; P = 0.37), total (6.1% vs 9.6%; P = 0.26) and serious adverse events, hospital mortality (3.4% vs 2.7%; P > 0.99), and ICU and hospital lenght of stay between the N-acetylcysteine and placebo groups. A post hoc subgroup analysis of patients (baseline creatinine level > 1.4 mg/dL [120 micromol/L]) showed a nonsignificant trend toward fewer patients experiencing postoperative renal dysfunction in the N-acetylcysteine group compared with the placebo group (25.0% vs 34.1%; P = 0.29). Conclusions: N-acetylcysteine did not prevent postoperative renal dysfunction, interventions, complications, or mortality in high-risk patients undergoing CABG surgery with CPB. Further research is required to identify CABG patients at risk for postoperative renal events, valid markers of renal dysfunction, and to estabilish renal thresholds associated with important clinical outcomes.

39. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial

Gomes VO, Poli de Figueredo CE, Caramori P et al.

Heart 2005 91 (6): 774-8.

Abstract Objective: To evaluate oral N-acetylcysteine in the prevention of contrast induced nephropathy (CIN) in patients at low to moderate risk undergoing cardiac catheterisation with ionic low osmolality contrast medium. Methods: In a multicentre double blind clinical trial 156 patients undergoing coronary angiography or percutaneous coronary intervention with serum creatinine > or = 106.08 micromol/l or creatinine clearence < 50 ml/min or diabetes mellitus were randomly assigned to receive N-acetylcysteine 600 mg orally twice daily for two days or placebo. Only low osmolality ionic contrast medium was used. Results: Sixteen patients developed CIN, defined as an increase of 44.2 micromol/l in creatinine in 48 hours: eight of 77 patients (10.1%) in the placebo group (p = 1.00). The mean (SD) change in serum creatinine was similar in both groups: 7.96 (35.36) micromol/l in the N-acetylcysteine group and 6.19 (25.64)micromol/l in the placebo group (p 0.67). No difference was observed in the change in endogenous creatinine clearence (-0.54 (10.4) ml/min vs -2.52 (12.3) ml/min, N-acetylcysteine and placebo, respectively, p = 0.28). Conclusion: Oral N-acetylcysteine did not prevent CIN in patients at low to moderate risk undergoing cardiac catheterisation with ionoc low osmolality contrast medium.

40. Zoledronic acid and renal toxicity: data from French adverse effect reporting database

Munier A, Gras V, Andrejak M et al.

Ann Pharmacother 2005 39 (7-8): 1194-7.

Abstract Background: Zoledronic acid-associated renal impairment leading to renal failure has been recently reported in a cohort of US patients. However, the presence of such toxicity in other populations has not yet been determined. Objective: To analyze French cases of zoledronic acid-associated nephrotoxicity. Methods: We evaluated available cases with acute deterioration of renal function associated with zoledronic acid therapy drawn from the French Adverse Event reporting System database until July 1, 2004. Results: We identified 4 men and 3 women between the ages of 52 and 70 years, with multiple myeloma or different types of metastatic cancer, who had experienced renal impairment during zoledronic acid therapy. Four patients developed de novo acute renal failure, while the other 3 patients experienced acute deterioration of preexisting chronic renal failure. Renal failure occured after various duration of zoledronic acid therapy (1-120 days). Three patients completely recovered and one partially recovered their previous renal function after discontinuation of zoledronic acid, but renal impairment was associated with a fatal outcome in 2 cases; the outcome of the other case was unknown. Our data confirm the previously reported risk factors for zoledronic acid-associated nephrotoxicity such as advanced cancer, multiple myeloma, preexisting renal failure, diabetes, hypertension, and concomitant use of nephrotoxic drugs. Conclusions: These cases emphasize the need for regular monitoring of renal function during zoledronic acid treatment, with particular attention to patients with preexisting impaired renal function.

VI. TRANSPLANTATION

1. Co-infection of polyomavirus-BK and cytomegalovirus in renal transplant recipients

Toyoda M, Puliyanda DP, Amet N et al.

Transplantation 2005 80 (2): 198-205.

Abstract Background: Polyomavirus-BK (BK) is a significant cause of allograft dysfunction in renal transplant recipients. Cytomegalovirus (CMV) and BK infection are though to be possible risk factors for one another, but no supporting data are yet available. Methods: The authors monitored BK and CMV infection by quantitative polymerase chain reaction (PCR) in 69 renal transplant recipients with serum creatinine elevation to determine the prevalence of co-infection. In addition, 150 adult renal transplant recipients were also retrospectively analyzed for both infections. Results: Of 69 recipients, 12 were plasma BK-PCR-positive. Eight of the showed high BK levels (>10 copies) and BK nephropathy. Six of the 12 were also CMV-PCR-positive compared with only 3 of 57 plasma BK-negative patients (50% vs 5.38%, P=0.001). Comparatively, the incidence of Epstein-Barr virus infection was similar in both groups (1 of 12 [8.3%] vs 2 of 57 [3,5%], P = not significant). In addition, retrospective analysis of CMV-PCR-positivity in 150 adult renal transplant recipients showed similar results (5 of 6 in BK-PCR-positive [83%] vs 8 of 14 BK-PCR-negative [5.6%], P=0.0001]. More plasma BK-PCR-positive patients had concomitant CMV infection than CMV-PCR-positive patients with BK infection. (5 of 6 [83%] vs 4 of 13 [31%], p=0.05). Conclusions: In conclusion, high plasma BK-positivty (>10) is significantly associated with BK nephropathy. Plasma BK-positivity is highly associated with co-infection of CMV, suggesting possible risk factors for one another. Therefore, detection of either infection strongly suggest the need to monitor for the other. This strategy may lead to the prevention of virus-induced complications by preemptive antiviral therapy in renal allografts.

2. Chronic renal allograft rejection: Pathophysiologic considerations

Joosten S, Sijpkens YWJ, van Kooten C et al.

Kidney Int 2005 68: 1-13.

Abstract Chronic rejection is currently the most prevalent cause of renal transplant failure. Clinically, chronic rejection presents by chronic transplant dysfunction, characterized by a slow loss of function, often in combination with proteinuria and hypertension. The histopathology is not specific in most cases but transplant glomerulopathy and multilayering of the peritubular capillaries are highly characteristic. Several risk factors have been identified such as young recipient age, black race, presensitization, histoincompatibility, and acute rejection episodes, espacially vascular rejection episodes that occur late after transplantation. Chronic rejection develops in grafts that undergo intermittent or persistent damage from cellular and humoral responses resulting from indirect recognition of alloantigens. Progression factors such as advanced donor age, renal dysfunction, hypertension, proteinuria, hyperlipidemia, and smoking accelerate deterioration of renal function. At the tissue level, senescence conditioned by iscemia/reperfusion (I/R) may contribute to the development of chronic allograft nephropathy (CAN). The most effective option to prevent renal failure from chronic rejection is to avoid graft from both immune and nonimmune mechanism together with non-nephrotoxic maintenance immunosuppression.

3. Chronic organizing microangiopathy in a renal transplant recipient

Wyatt CM, Dikman S, Sehgal V et al.

Nephrol Dial Transplant 2005 20: 1734-7.

Abstract Thrombotic microangiopathy (TMA) not an uncommon but potentially serious complication of transplantation, occurs in 3-15% of renal transplant recipients. *De novo* post-transplant TMA is mostly due to calcineurin inhibitor toxicity. Histologically, TMA is characterized by glomerular endocapillary damage with subendothelial accumulation of amorphous material. Narrowing or occlusion of capillaries with intravascular fibrin thrombi and fragmented erythrocytes is common. Similar changes involve arterioles and arteries. Post-transplant TMA can be isolated to the allograft or can present with clinical and laboratory evidence of systemic TMA, including fever, haemolytic anaemia and renal failure. Intravascular haemolysis leads to the presence of schistocytes on peripheral blood smear, increased lactate dehydrogenase (LDH), and decreased haptoglobin levels in the systemic firm of post-transplant TMA, which is often reffered to as haemolytic-uraemic syndrome (HUS). Both localized and systemic TMA can present with acute renal failure, and both have been associated with decreased graft survival. Here we use the descriptive term TMA to refer to both localized and sytemic forms of post-transplant TMA, as well as to systemic forms of TMA in the general population, including HUS and thrombotic thrombocytopenic purpura (TTP). Recurrence of TMA following clinical resolution has been described in renal transplant recipients with pre-transplant TMA and in patients rechallenged with calcineurin inhibitor following an episode of calcineurin inhibitor-induced TMA. The role of the initial endothelial insult in recurrent disease is unclear, and the significance of residual histological changes is not well described. Because the organizing phase of TMA may resemble chronic transplant glomerulopathy, it is unclear hoe often post-transplant TMA evolves into the fibrotic organizing phase. We present serial renal biopsies from a patient with acute humoral rejection and later development of malignant hypertension and systemic TMA, in whom intervening biopsies revealed fibrotic microvascular changes attributed to chronic organizing microangiopathy.

4. Recurrent glomerulonephritis in the renal allograft: un update of selected areas

Couser W

Exp Clin Transplant 2005 3 (1): 283-8.

Abstract Glomerular diseases, including diabetes and various forms of glomerulonephritis, account for more than 70% of patients undergoing renal transplantation. Among these patients, more than 40% develop significant proteinuria, and around 15% develop persistent nephrotic syndrome. The most common cause of posttransplantation proteinuria is chronic allograft nephropathy (60%), followed by recurrent (15%) and de nove (10%) glomerulonephritis. Persistent proteinuria is associated with a significantly reduced rate of graft survival but often can be controlled with non-disease specific therapy
including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with favorable effects on long-term prognosis. Recurrent or de novo glomerulonephritis occurs in 6%.20% of patients overall and is more common in patients transplanted with glomerulonephritic organs. Glomerulonephritis in the allograft is also associated with a reduction in long-term (5-year) graft survival (40% vs 70%). The most common disease associated with allograft glomerulonephritis and their recurrence rates in transplantation patients are idiopathic focal glomerular sclerosis (20%-30%), IgA nephropathy (25%), membranoproliferative glomerulonephritis (type 1, 25%; type 2, 80%), membranous nephropathy (30%), and hemolytic-uremic syndrome (classic, 10%; atypical, 40%; familial, 60%). This article reviews new developments in the understanding of 3 of these diseases - focal glomerular sclerosis, membranous nephropathy, and hemolytic-uremic syndrome - as they relate to the incidence of recurrence, the effects of recurrence on graft survival, risk factors for recurrences, and management issues for nephrologists caring for patients with renal allografts. Proper donor selection, early diagnosis in high-risk patients, and appropriate management can prolong graft survival and improve long-term outcomes.

5. New insights into the pathogenesis and the therapy of recurrent focal glomerulosclerosis

Vincenti F, Ghiggeri GM

Am J Transplant 2005 5 (6): 1179-85.

Abstract Recurrent focal glomerulosclerosis (FSGS) in renal allografts has remained a frustrating and enigmatic disease. Recent studies on gene mutations encoding podocin and other components of the slit-diaphragm in patients with native kidney nephrotic syndrome have underscored the heterogeniecity of the idiopathic form of FSGS. While familial FSGS rarely recurs following transplantation, the sporadic variety of FSGS is associated with a 30% recurrence rate. The patients with the sporadic variety of FSGS who have homozygous or complex heterozygous podocin mutations have a low recurrence rate. In the other patients with sporadic FSGS, a more complex and likely multifactorial etiology accounts for the recurrence of FSGS. The role of CD80 expression on podocytes is intriguing but requires confirmation in kidney biopsies of patients with recurrent FSGS. Recent findings on podocin genomics, the permeability factor and CD80 expression may ultimately lead to a better understanding of recurrent FSGS as well as a more effective approach to its prevention and treatment.

6. Recurrence of membranoproliferative glomerulonephritis type II in renal allografts: The North American Pediatric Renal Transplant Cooperative Study experience

Braun MC, Stablein DM, Hamiwka LA et al.

J Am Soc Nephrol 2005 16 (7): 2225-33.

Abstract Membranoproliferative glomerulonephritis type II (MPGN II) is an uncommon form of complement-dependent acquired renal disease. Although it has been recognized since the 1970s that MPGN II recurs almost universally in renal transplants, date regarding the long-term consequences of disease recurrence are limited. Therefore, a retrospective comparative analysis of 75 patients with MPGN II contained in the North American Pediatric Renal Transplant Cooperative Study transplantation database was performed. Five-year graft survival for patients with MPGN II was significantly worse (50.0 +/- 7.5%) compared with database as a whole (74.3 +/- 0.6%; P < 0.001). Living related donor organs had a significantly better 5-yr survival (65.9 +/- 10.7%) compared with cadaveric donor organs (34.1 +/- 9.8%; p = 0.004). The primary cause of graft failure in 11 (14.7%) patients was recurrent disease. Supplemental surveys were obtained on 29 (38%) of 75 patients. Analysis of these data indicated that recurrent disease occured in 12 (67%) of the 18 patients with posttransplantation biopsies. Although there was no correlation between pretransplantation presentation, pre- or posttransplantation C3 levels, and either disease recurrence or graft failure, there was a strong association between heavy proteinuria and disease recurrence. The presence of glomerular crescents in allograft biopsies had a significant negative correlation with graft survival. At least follow-up, patients with recurrent disease had a significantly higher serum creatinine and qualitatively more proteinuria than patients without biopsy-proven disease. These data indicate that recurrent MPGN II has a significantly negative impact on renal allograft function and survival.

7. Transplantation and 6-month follow-up of renal transplantation from a donor with systemic lupus erythematosus and lupus nephritis

Schwartzman MS, Zhang PL, Potdar S et al.

Am J Transplant 2005 5 (7): 1772-6.

Abstract Transplantation of kidney with pre-existing glomerulonephritis (GN) has rarely been reported. Little is known of the subsequent evolution of donor pathology in the recipient. We report a transplant using a donor with systemic lupus erythematosus (SLE) and a history of remote acute renal failure but normal renal function at death. Although the screening harvest biopsy was unremarkable, time zero post-implantation renal biopsy showed evidence of lupus nephritis (LN). Sequential protocol demonstrated gradual resolution of the donor pathology, and renal function was stable despite severe cardiac disease in the recipient. Studies

examining the role of functional and biopsy data on outcomes in expanded criteria renal transplantation are reviewed, and the limits of guidance from use of this data are discussed. Pre-existing mild GN may not be an absolute donor exclusion for candidates willing to accept expanded criteria donors. Use of expanded pool kidneys should be guided by functional, biopsy and demographic information, as no single factor alone predicts outcome.

8. Impact of statin treatment on 1-year functional and histologic renal allograft outcome

Masterson R, Hewitson T, Leikis M et al.

Transplantation 2005 80 (3): 332-8.

Abstract Background: Statins are antilipidemic agents that exhibit a variety of cellular effects independent of their lipid-lowering action. A retrospective study was undertaken to establish the impact of statins on graft outcome in the first year posttransplantation. Methods: Data from patients with uniform immunosuppression (cyclophosphamide, mycophenolate mofetil, and prednisolone) who underwent transplantation at the authors' unit from 1997 to 2002 were reviewed. Patients prescribed statins were compared with those not on a statin. Mean change in creatinine clearence (CrCl) from 3 to 12 months posttransplantation was calculated. Histomorphometric analysis was used quantify fractional interstitial area and collagen III deposition in matched preperfusion and 12-month protocol biopsy specimens. Results: Seventy-seven patients met study criteria: statin, n=44 patients; nonstatin, n=33 patients. Median time to commencing a statin was 5 weeks. At 3 months, CrCL (+/-SEM) was similar: 51.6+/-2.9 mL/min (statin) versus 51.3+/-1 mL/min (nonstatin). At 12 months, the mean change in CrCL was 4.1+/-1 mL/min (statin) compared with -2.0+/-1.8 mL/min (nonstatin), resulting in a difference of 6.13 mL/min at 12 months (P<0.005). Mean perfusion fractional interstitial areas were similar (23.9+/-1.6%; P=not significant [NS]. On 12-month biopsy specimens, the fractional interstitial area had increased to 34+/-3.2% in the nonstatin group (P<0.005), with no change in the statin group. Interstitial collagen III deposition was similar in preperfusion biopsy specimens (10.4+/-1%; P=NS), but at 12 months was significantly greater in the nonstatin group (17.6+/-1%; P<0.05). Conclusions: Early introduction of statins may be associated with improved 1-year graft outcome.

9. Effects of sirolimus on mesangial cell cholesterol homeostasis: a novel mechanisms for its action against lipid-mediated injury in renal allografts

Varghese Z, Fernando R, Moorhead JF et al.

Am J Physiol Renal Physiol 2005 289 (1): F43-8.

Abstract Lipoprotein abnormalities are present in a high proportion of renal transplant patients. It is accepted that dyslipidemia is associated with atherosclerosis and in the progression of renal disease. Lipid abnormalities may also play a significant role in the development of chronic allograft nephropathy. Sirolimus was found to have an atherosclerotic effect in the apolipoprotein E-knockout mice model of hyperlipidemia through its antiproliferative effects. As lipid-mediated renal injury is important in the pathogenesis of glomerulosclerosis which shares common pathogenic mechanisms with atherosclerosis, in this study we have tested the hypothesis that sirolimus prevents lipid-mediated renal injury through the modulation of cholesterol homeostasis of mesangial cells and its anti-inflammatory effects on macrophages. We demonstrated that sirolimus reduced lipid accumulation, as measured by oil red O staining in human mesangial cells (HMCs). Using real-time PCR, we screened the mRNA expression of lipoprotein receptors. Sirolimus significantly suppressed LDL and VLDL receptors and CD36 gene expression. It also increased cholesterol efflux from HMCs by increasing peroxisome proliferator-activated receptor-alpha (PPARalpha), PPARgamma, liver X receptor-alpha, and ATP binding cassette A1 (ABCA1), gene expression. Sirolimus overrode the suppression of cholesterol efflux and ABCA1 gene expression induced by the inflammatory cytokine IL-1beta. Furthermore, sirolimus significantly inhibited inflammatory cytokines IL-6 and TNF-alpha production in macophages. These data suggest that sirolimus may prevent cellular cholesterol accumulation even in the

presence of hyperlipidemia and inflammation, by regulating both cholesterol homeostasis and inflammatory responses.

10. Effects of antioxidant supplementation on blood cyclosporin A and glomerular filtration rate in renal transplant recipients

Blackhall ML, Fassett RG, Sharman JE et al.

Nephrol Dial Transplant 2005 20: 1970-5.

Abstract Background: Transplant recipients have elevated oxidative stress, which has prompted suggestions that supplementary antioxidants may be beneficial. However, only a small number of clinical trials have investigated antioxidant supplementation in transplant recipients, with very few data on their effects on patients' immunosupressive therapy. Methods: A randomized placebo-controlled single-blind crossover trial was conducted in 10 renal transplant recipients (RTRs) taking cyclosporin A (CsA) as part of their immunosuppressive therapy. Each phase of the trial lasted 6 months, with a 6 month wash-out period in between. During one of the phases, patients consumed a tablet twice per day which delivered 400IU/day of vitamin E, 500mg/day of vitamin C and 6mg/day of ß-carotene. Results: During antioxidant supplementation, there was no change in CsA dose. Antioxidant supplementation resulted in a significant decrease ($P<0.05$) in blood trough CsA by 24% (mean±SD, pre- 127.3±38.9, post- 97.2±30.7 ug/ml) compared with no change while taking the placebo (pre- 132.2±50.6, post- 138.6±56.0 ug/ml). The glomerular filtration rate was significantly ($P<0.05$) improved by 12% during antioxidant supplementation)pre- 66.9±20.7, post- 750.0±20.1 ml/min/1,72m*2) with no change during the placebo phase (pre- 66.8±11.8, post- 66.7±16.1 ml/min/1,73m*2). There were no significant differences ($P>0.05$) in markers of oxidative stress (malondialdehyde, susceptibility of plasma to oxidation) or plasma antioxidant enzymes. Conclusion: In CsA-treated RTRs, antioxidant supplementation decreased blood CsA, which may affect adequacy of immunosuppression.