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

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I. EPIDEMIOLOGY

1. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications

Schieppati A, Remuzzi G.

Kidney Int Suppl 2005 (98): S7-S10.

2. A lethal tetrad in diabetes: hyperglycemia, dyslipidemia, oxidative stress, and endothelial dysfunction

Yu Y, Lyons TJ.

Am J Med Sci 2005 330 (5): 227-32.

3. A global burden of group A streptococcal diseases

Carapetis JR, Steer AC, Mulholland EK, Weber M.

Lancet Infect Dis 2005 5 (11): 685-94.

4. Racial differences in renal arteriolar structure in children with minimal change nephropathy

Rostand SG, Cross SK, Kirk KA, Lee Jy, Kuhlmann A, Amann K.

Kidney Int. 2005 68 (3): 1154-60.

5. Nephrotic syndrome in African children: lack of evidence for 'topical nephrotic syndrome'?

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6. The MTHFR 677TT and 677CT/1298AC genotypes in Cypriot patients may be predisposing to hypertensive nephrosclerosis and chronic renal failure

Koupepidou P, Deltas C, Christofides TC, Athanasiou Y, Zouvani I, Pierides A.

Int Angiol 2005 24 (3): 287-94.

7. Henoch Schonlein purpura in childhood: Epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature

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Finne P, Reunanen A, Stenman S, Groop PH, Grönhagen-Riska C.

JAMA 2005 294: 1782-7.

9. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis

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Diabetologia 2005 48: 1749-55.

10. The changing epidemiology of diabetic microangiopathy in type 1 diabetes

Rossing P.

Diabetologia 2005 48 (8): 1439-44.

11. Epidemiology of diabetic nephropathy in Spain

Martinez-Castelao A, De Alvaro F, Gorriz JL.

Kidney Int Suppl 2005 99: S20-4.

12. End-stage renal disease in Brazil: epidemiology, prevention, and treatment

Oliveira MB, Romao JE, Zatz R.

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13. Prevalence of chronic kidney disease in an urban Mexican population

Amato D, Alvarez-Aquilar C, Castaneda-Limones R, Rodriguez E, Avila-Diaz M, Arreola F, Gomez A, Ballesteros H, Becerril R, Paniagua R.

Kidney Int Suppl 2005 (97): S11-7.

14. Detection of early nephropathy in Mexican patients with type 2 diabetes mellitus

Cueto-Manzano AM, Cortes-Sanabria L, Martinez-Ramirez HR, Rojas-Campos E, Barragan G, Alfaro G, Flores J, Anaya M, Canales-Munoz JL.

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II. ETIOLOGY

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Padiyar A, Sedor JR.

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2. Molecular genetic approaches for studying the etiology of diabetic nephropathy

Ng DP, Krolewski AS.

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3. Carnosine as a protective factor in diabetic nephropathy. Association with a leucine repeat of the carnosinase gene CNDP1

Janssen B, Hohenadel D, Brinkkoetter P, Peters V, Rind N, Fischer C, Rychlik I, Cerna M, Romzova M, de Heer E, Baelde H, Bakker SJL, Zirie M, Rondeau E, Mathieson P, Saleem MA, Meyer J, Köppel H, Sauerhoeffer S, Bartram CR, Nawroth P, Hammes HP, Yard BA, Zschocke J, van der Woude FJ.

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Berggren R, Batuman V.

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8. Crescentic glomerulonephritis associated with bacterial endocarditis – antibiotics alone may be sufficient. A case report

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Chin G, Luxton G, Harvey JM.

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Yasuhara D, Naruo T, Taguchi S, Umekita Y, Yoshida H, Nozoe SI.

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J Eur Acad Dermatol Venerol 2005 19 (5): 617-20.

19. Nephrotic syndrome and renal failure after allogenic stem cell transplantation: novel molecular diagnostic tools for a challenging differential diagnosis

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III. PATHOGENESIS

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Ikezumi Y, Suzuki T, Hayafuji S, Okubo S, Nikolic-Paterson DJ, Kawachi H, Shimizu F, Uchiyama M.

Nephrol Dial Transplant 2005 20: 2704-13.

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Nangaku M, Couser WG.

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Okada H, Kalluri R.

Curr Mol Med 2005 5 (5): 467-74.

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Wang EH, Goh YB, Moon IS, Park CH, Lee KH, Kang SH, Kang CS, Choi YJ.

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15. Methylenetetrahydrofolate reductase gene polymorphysms in essential hypertension relation with the development of hypertensive end-stage renal disease

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16. Prostacyclin signaling in the kidney: implications for health and disease

Nasrallah R, Hebert RL.

Am J Physiol Renal Physiol 2005 289 (2): F235-46.

17. Puberty and chronic kidney disease

Lane PH.

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18. Class IV-S versus class IV-G lupus nephritis: Clinical and morphologic differences suggesting different pathogenesis

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Bilge I, Sirin A, Agachan B, Emre S, Sadikoglu B, Yilmaz H, Sucu A, Isbir T.

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32. Implication of peritubular capillary loss and altered expression of vascular endothelial growth factor in IgA nephropathy

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C O N T E N T S

Part Two

SECTIONS

TITLE OF PUBLICATIONS – AUTHORS – SUMMARY OF PUBLICATIONS

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Part Two

I. EPIDEMIOLOGY

1. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications

Schiepatti A, Remuzzi G.

Kidney Int Suppl 2005 (98): S7-10.

The impact of chronic kidney disease (CKD) on the global burden of disease is probably underestimated by current methods of evaluation. However, CKD are emerging as a major health problem. First, the costs of renal replacement therapy are excedingly high and are consuming a significant proportion of health care budgets of developed countries, while in developing countries are out of reach. Second, complex interaction are clearly emerging between chronic kidney, cardiovascular disease, and diabetes.

2. A lethal tetrad in diabetes: hyperglycemia, dsylipidemia, oxidative stress, and endothelial dysfunction

Yu Y, Lyons TJ.

Am J Med Sci 2005 330 (5): 227-32.

This paper adresses the consequences of diabetes and obesity, diseases that have become epidemic in our society, particularly in the past 20 years. Specifically, it summarizes current knowledge about some of the risk factors and mechanisms for the vascular complications of diabetes. These complications can be broadly divided into microvascular disease, such as diabetic retinopathy and diabetic nephropathy, and macrovascular disease, such as accelerated atherosclerosis, and they are the main cause for morbiditiy and premature mortality among diabetic patients. The roles of hyperglycemia, dyslipidemia and dyslipoproteinemia, oxidative stress, and endothelial dysfunction will be considered. Finally, the „treatment gap" will be addressed. This gap refers to our failure to achieve currently accepted goals to reduce eatabilished risk factors for complications in the clinical management of diabetic patients.

3. The global burden of group A streptococcal diseases

Carapetis JR, Steer AC, Mulholland Ek et al.

Lancet Infect Dis 2005 5 (11): 685-94.

The global burden of disease caused by group A streptococcus (GAS) is not known. We review recent population-based data to estimate the burden of GAS diseases and highlight deficiencies in the available data. We estimate that there are at least 517.000 deaths each year due to svere GAS diseases (eg, acute rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis, and invasive infections). The prevalence of severe GAS disease is at least 18.1 million cases, with 1.78 million new cases each year. The greatest burden is due to rheumatic heart disease, with a prevalence of at least 15.6 million cases, with 282.000 new cases and 233.000 deaths each year. The burden of invasive GAS diseases is unexpectedly high, with at least 663.000 new cases and 163.000 deaths each year. In addition, there are more than 111 million prevalent cases of GAS pyoderma, and over 616 million incident cases per year of GAS pharingytis. Epidemiological data from developing countries for most diseases is poor. On a global scale, GAS is an important cause of morbidity and mortality. These data emphasise the need to reinforce current control strategies, develop new primary prevention strategies, and collect better data from developing countries.

4. Racial differences in renal arteriolar structure in children with minimal change nephropathy

Rostand SG, Cross SK, Kirk KA et al.

Kidney Int 2005 68 (3): 1154-60.

Background African Americans are at increased risk for hypertension and chronic renal disease.

Some data suggest this results from renal microvascular disease. The aim of this study was to determine if renal vascular changes were more pronounced in African Americans, were independent of blood pressure, and occured in early childhood. Methods We performed morphometric analysis on small cortical arterias from 44 renal biopsies done in African American and white children (mean age 8.4 +/- SD 5.0 years) with minimal change nephropathy. Outer and inner vessel diameter were measured and wall : lumen and wall : outer diameter ratios (WT/OD) calculated. Clinical data on blood pressure, steroid use, serum creatinine, gender, age, and proteinuria were abstracted by chart review. A z score for systolic and diastolic blood pressure was calculated. Follow-up clinical data were available for 11 children. Data were compared uring analysis of covariance (ANCOVA) and t test for paired data. Results Lumen diameters of African Americans were 3.1 mum (23%) smaller that those of white children (P=0.024). Similarly, their WT/OD was greater than in the whites, 0.31 +/- 0.03 vs 0.28 +/- 0.02 (P=0.048). These changes were independent of age, steroid use, systolic blood pressure and diastolic blood pressure z scores. Follow-up data showed a rise in serum creatinine (> 50%) in five patients, +1.42+/-0.79 mg/dL (P=0.016), of whom four were African American. There was no change in blood pressure. Conclusion The renal arterioles of African American children with minimal change nephropathy exhibit significantly smaller lumens and thicker walls than white children. The changes occur very early in life and independent of age, blood pressure, and steroid use. Such changes may contribute to the African American predispisition to chronic renal disease and hypertension.

5. Nephrotic syndrome in African children: lack of evidence for 'tropical nephrotic syndrome'?

Yao Doe J, Funk M, Mengel M et al.

Nephrol Dial Transplant 2005 Dec 2 [Epub ahead of print]

Background Infections such as malaria, schistosomiasis, hepatitis B and HIV have beeen suggested as major causes of the nephrotic syndrome (NS) in African children. We retrospectively analysed the course of the NS in 32 children from Ghana and reviewed the literature on NS from different African countries for the presence of 'the tropical nephrotic syndrome'. Methods Thirty-two children (22 boys, 10 girls, median age 12 years, range 1-18 years) with NS were treated from 2000-2003 at Battor Hospital, Ghana. Thirteen out of 32 children underwent a renal biopsy which was investigated by light, immune and electron microscopy. All 32 patients were initially treated with oral prednisone (PRED) therapy (29 with standard therapy for 8 weeks and three individually tailored), and steroid-resistant children received also intravenous methylprednisolone pulses (three children) or oral cyclophosphamide (two children). Results All patients fulfilled the clinical and laboratory criteria of a NS. The initial median serum creatinine was 65 micromol/l (range 44-133 micromol/l). Renal biopsy was performed in 13/32 children and revealed focal and segmental glomerulosclerosis (FSGS) in 10 patients, minimal change disease (MCNs) in two and no conclusive results in one patient. Glomerular immune complex deposition was absent in all biopsies. After treatment with PRED, oedema disappeared in 24/32 patients; however, proteinuria normalized in 16/32 patients only. The NS relapsed in 9/16 steroid sensitive patients after cessation of PRED therapy, and two children were frequent relapsers. The steroid-resistant NS did not respond to an intensified immunosuppression in 5/16 children receiving methylprednisolone or cyclophosphamide. Five out of 32 children died, all were steroid resistant. Conclusion There was no evidence for a dominating role of steroid-resistant 'topical glomerulopathies' in children with a NS in Ghana. Similar to South Africa, focal and segmental glomerulosclerosis (FSGS) and minimal change disease were the most frequent findings on histology. Contrary to Nigeria, membrano-

proliferative glomerulonephritis was not found in these patients. We conclude from this data and from the literature that the histological pattern of NS may vary between different African countries. Concerning therapy of NS under tropical conditions, we emphasize that despite the limited therapeutic facilities half of these patients may benefit from corticosteroids; however, steroid resistance and FSGS resulted in a high mortality.

6. The MTHFR 677TT and 677CT/1298AC genotypes in Cypriot patients may be predisposing to hypertensive nephrosclerosis and chronic renal failure

Koupepidou P, Deltas C, Christofides TC et al.

Int Angiol 2005 24 (3): 287-94.

Aim The homozygous 677TT mutation of the MTHFR gene has been linked to deep vein thrombosis and to arterial atherosclerotic events of the coronary carotid and peripheral arteries. Its putative association with renal arteriosclerosis and chronic renal failure (CRF) in the presence of hypertensive nephrosclerosis is yet to be investigated. Methods Two hundred and twenty-one Greek-Cypriot patients with CRF from one single renal unit in Cyprus were divided 6 diagnostic categories: 49 due to chronic glomerulonephritis (22.2%), 43 due to diabetes mellitus (19.4%), 26 due to autosomal dominant polycystic kidney disease (11.8%), 30 due to essential hypertension leading to nephrosclerosis (13.6%), including 4 patients with primary malignant hypertension, 32 with other rarer causes of CFR (14.5%) and 41 of uncertain etiology (18.5%). These 221 CRF patients had MTHFR C677T and A1298C genotypes analyzed by the polymerase chain reaction and agarose gel electrophoresis after restriction enzyme digestion. The frequency of the homozygous states 677TT and 1298CC and the double heterozygous 677/1298AC were compared to those of 210 unrelated normal local controls. Results A statistically significant increase in the frequency of the 677TT genotype compared to controls was only found in the hypertensive nephrosclerosis CFR sub-group of patients. The prevalence rate of the 677TT genotype was 46.7% (controls 17.6%, P=0.0007). Combined together the homozygous 677TT and double heterozygous 677CT/1298AC genotypes were found in 86.7% of the hypertensive nephrosclerotic CRF patients, compared to 46.6% in normal controls (P=0.0001). Conclusion The findings support the hypothesis that Caucasian patients with essential hypertension, homozygous for 677TT or doubly heterozygous for 677CT/1298AC genotypes, are predisposed to develop hypertensive nephrosclerosis and CRF.

7. Henoch Schonlein purpura in childhood: Epidemiological and clinical analysis of 150 cases over 5-year period and review of literature

Trapani S, Micheli A, Grisolia F et al.

Semin Arthritis Rheum 2005 35 (3): 143-53.

Objective To examine epidemiological, clinical, and outcome in Italian children affected with Henoch Schonlein purpura (HSP). Methods Retrospective study of children discharged with a

diagnosis of HSP from the Meyer Children's Hospital, between 1998 and 2002. Epidemiological, clinical, laboratory data, treatment, and outcome were collected by reviewing medical charts. One year after data collection, the children's parents were interviewed by telephone about the outcome. Results 150 children entered the study: M:F = 1.8:1; mean age 6.1 +/- 2.7 years. At onset, purpura was present in all cases, arthritis/arthralgias in 74%, abdominal involvement in 51%, scrotal edema in 13%, renal involvement in 54%, severe nephropathy in 7%, acute renal insufficiency in 2%, and intussusception in 0.6%. Purpura was presenting symptom in 74%, arthritis in 15%, and abdominal pain in 12%. The most frequent laboratory abnormalities were high-erytrocyte sedimentation rate (ESR) (57%), hyper-IgA (37%), and proteinuria (42%). All patients recovered within 2 months. Recurrences, verified in 35%, were correlated with high ESR values and corticosteroid (CS) treatment, independently from other variables. After a mean 2.5-years follow-up, 2 patients had hematuria with normal renal function. Conclusion Epidemiological and clinical findings in our cohort are similar to those in the literature, even though the mean disease duration was shorter than previously reported. Relapses occured significantly more frequently in children treated with CS. This finding supports the recommendation to limit the use of steroids to a carefully selected group of HSP children. The prognosis was excellent; severe nephropathy was found in a small percentage of the children, at follow-up all had normal renal function. Thus, our study confirms the benignity of HSP in Italian children, especially regarding renal outcome.

8. Incidence of end-stage renal disease in patients with type 1 diabetes

Finne P, Reunanen A, Stenman S et al.

JAMA 2005 294: 1782-7.

Context End-stage renal disease (ESRD) is one of the most severe complications of type 1 diabetes. Yet, data on patients' risk of developing ESRD are sparse. Objectives To estimate the long-term developing ESRD and to assess how age at diagnosis of diabetes, time period of diagnosis, and sex affect the risk. Design, Setting, and Patients A cohort of all patients younger than 30 years diagnosed as having type 1 diabetes in Finland in 1965-1999 (n=20.005) was identified from the Finnish Diabetes Register. The cohort was followed up from diagnosis of diabetes until development of ESRD (dialysis or kidney transplantation as identified from the Finnish Registry for Kidney Diseases), death, or end of follow-up on December 31, 2001. Main Outcome Measure Cumulative incidence of ESRD, accounting for death as a competing risk. Results The cohort was followed up for maximally 37 years, with a median of 16.7 years. During 346851 person-years, 632 patients developed ESRD. The cumulative incidence of ESRD was 2.2% at 20 years and 7.8% at 30 years after diagnosis. The risk of developing ESRD was lowest in patients whose diagnosis occured at younger than 5 years. The risk of ESRD was lower for patients diagnosed as having type 1 diabetes in later years. The risk did not differ significantly between sexes. Conclusions With regard to ESRD, the prognosis of type 1 diabetes has improved during the past decades. Children diagnosed as having diabetes before age 5 years have the most favorable prognosis. Overall, incidence of ESRD appears to be lower than previously estimated.

9. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-

diabetic participants in the HOPE study: a prospective epidemiological analysis

Gerstein HC, Pogue J, Mann JFE et al.

Diabetologia 2005 48: 1749-55.

Abstract Aims/hypothesis Emerging data suggest that different indices are risk factors for clinical events. The aim of this analysis was to investigate the relationship between fasting plasma glucose or glycated haemoglobin (GHb) levels and incident cardiovascular (CV) outcomes, death, heart failure and overt nephropathy in diabetic and non-diabetic individuals enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study. Materials and methods The adjusted 4.5-year risk of CV events (myocardial infarction or stroke or CV death), heart failure, death and overt nephropathy was analysed in relation to baseline and updated GHb levels (in 3.529 diabetic HOPE study participants) and baseline fasting plasma levels (in 1.937 non-diabetic participants). Results In diabetic participants, a 1% absolute rise in the updated GHb predicted future CV events (relative risk [RR]=1.07, 95% CI 1.01-1.13; p=0.014), death (RR=1.12, 95% CI 1.05-1.19; p=0.0004), heart failure (RR=1.20, 95% CI 1.08-1.33, p=0.0008) and overt nephropathy (RR=1.26, 95% CI 1.17-1.36; p<0.0001) after adjusting for age, sex, diabetes duration, blood pressure, WHR, hyperlipidaemia and ramipril. Similarly, a 1 mmol/l rise in fasting plasma glucose was related to an increased risk of CV outcomes (RR=1.09, 95% CI 1.05-1.13; p<0.0001), death (RR=1.06, 95% CI 1.01-1.12; p=0.017), heart failure (RR=1.16, 95% CI 1.06-1.13; p=0.0007) and overt nephropathy (RR=1.34, 95% CI 1.23-1.45; p<0.0001) in the group composed and non-diabetic individuals. The significant relationship between fasting plasma glucose and CV outcomes persisted after adjustment for diabetes status (RR=1.06, 95% CI 1.00-1.12; p=0.043). Conclusion/interpretation There is an independent progressive relationship between indices of glycaemia and incident CV events, renal disease and death. Clinical trials of glucose lowering to prevent these outcomes in diabetic and non-diabetic individuals are indicated.

10. The changing epidemiology of diabetic microangiopathy in type 1 diabetes

Rossing P.

Diabetologia 2005 48 (8): 1439-44.

Diabetic microvascular complications in the kidney and the eye are a major burden for diabetic patients due to increased morbidity and mortality. Furthermore, diabetic nephropathy is the leading cause of end-stage renal disease and diabetic retinopathy is the leading cause of blindness in younger patients, representing a major public health concern. During the past two decades beneficial effects of, particular, aggressive antihypertensive control and strict glycaemic control have been demonstrated in randomised controlled clinical trials. Technolgical improvements in diabetes care have made good metabolic control easier to achieve. Has this led to an improved prognosis? In observational studies from dedicated centres, a decrease from 47 to 13% has been reported in the incidence of proliferative diabetic retinopathy after 20-25 years of diabetes, and the incidence of overt diabetic nephropathy after 20 years has decreased from 28 to 5.8%. Even functional and morphological remission of diabetic nephropathy has been reported. Despite this, recent population-

based studies have failed to demonstrate a decrease in the incidence of blindness caused by diabetes, and the incidence of end-stage renal disease has progressively increased. This may, in part, be the result of a combination of increasing numbers of diabetic patients and a lag phase between improvement in management and a decline in end-stage complications. It is of concern, however, that the results from specialised centers may not apply to routine diabetes care. It is, therefore, mandatory that the beneficial effects of pharmacological and non-pharmacological interventions demonstrated in clinical trials and recommended by treatment guidelines are translated into clinical practice to ensure a widespread improvement in prognosis.

11. Epidemiology of diabetic nephropathy in Spain

Martinez-Castelao A, De Alvaro F, Gorriz JL.

Kidney Int Suppl 2005 (99): S20-4.

Background The incidence of diabetes mellitus (DM) has increased persistently in recent years and is becoming an epidemic. Some have estimated that 4.4% of the world's population will be diabetic by the year 2030. The increase incidence of DM has been accompained by an increased incidence in diabetic nephropathy (DN), the main cause of end-stage renal disease. Methods and Resutls In 1996, a pharmaco-economic study estimated that 162,000 people in Spain had type 1 DM and 1,354,900 had type 2 DM. More recent studdies have estimated that 6% to 10% of the Spanish population might be diabetic. This percentage is higher in some autonomous communities, such as Canarias, in which 12% of the population is thought to have DM. Based on these studies, we estimate that more than 33,000 residents of Canarias have DN associated with type 1 DM, and more than 405,000 have DN associated with type 2 DM. The percentage of diabetic patients starting renal replacement therapy each year is currently around 21% in Spain but much higher (35%) in Canarias, which equates to 78 patients per million population (pmp) per year. In Catalonia, the number of DM patients entering renal replacement therapy has increased from 8.6 pmp per year in 1984 to 32.4 pmp per year in 2003. We estimate that the systematic application of converting enzyme inhibitors or angiotensin receptor blockers could save than 2.690 million over 15 years in Spain. Conclusion This epidemic could be prevented, or its impact reduced, through multifactoral and multidisciplinary early intervention, under the observance of guides, Spanish consensus documents, and clinical practice recommendations, together with an integrated educational program aimed at people with diabetes and the improvement of the standard of medical care.

12. End-stage renal disease in Brazil: epidemiology, prevention and treatment.

Oliveira MB, Romao JE, Zatz R.

Kidney Int Suppl 2005 (97): S82-6.

Brazil is one of the largest and most populous nations in the world, ranking among the 5 largest economies in the Americans and among the 15 largest economies in the world. However, Brazil is

still plaqued by social problems such as the persistence of poverty and immense deficiencies in its health system. Currently, there are approximately 390 patients on chronic renal replacement therapy (RRT) per million population, about one third the US prevalence, which suggest that end-stage renal disease is either underdiagnosed or undertreated. The epidemiology of renal disease in the small remaining native Brazilian population is largely unknown. However, it is likely that the prevalence of renal disease is low among at least 2 tribes: the Yanomamis in northern Brazil and the Xingu Indians in central Brazil. Sodium intake very low, physical activity is intense, and the prevalence of hypertension and cardiovascular disease is negligible these people, which stresses the potential pathogenic importance of so-called civilized habits. There is currently no conclusive evidence that African descendants or any other Brazilian ethnic minorites are especially vulnerable to renal disease. Access to RRT in Brazil is universal. However, because both the end-stage renal disease population and operational RRT costs are steadily increasing, the system may face severe limitations in the near future. Much effort is needed to limit the prevalence of renal disease, to detain or retard the progression of chronic nephropathies, and to ensure that high-qulity RRT will remain available to all those who need it.

13. Prevalence of chronic kidney disease in an urban Mexican population

Amato D, Alvarez-Aquilar C, Castaneda-Limones R et al.

Kidney Int Suppl 2005 (97): S11-7.

Background The present study was primarily designed to asses the prevalence of chronic kidney disease in Mexican urban population residing in Mexico and to evaluate certain biologic and socioeconomic conditions as risk factors for the development of renal disease. Methods A population-based cross-sectional survey was conducted, which included 3564 patients of either gender aged >18 years, who were randomly selected from lists of patients assigned to primary care facilities in the city of Morelia. A questionnaire about personal current health status, kidney disease, diabetes, hypertension, or heart disease in close relatives, anthropometric and blood pressure measurements, and blood and urine samples to measure glucose, blood urea nitrogen, and creatinine was obtained for each patient. Creatinine clearence (Ccr) was calculated by the the Cockcroft-Gault formula. Patients were classified in 1 of the 5 Ccr categories estabilished by the Kidney Disease Outcomes Quality Initiative guidelines. Results The prevalence rate of Ccr < 15 mL/min was 1142 per million population, and that of Ccr < 60 mL/min 80.788 per million population. Alcohol and tobacco consumption, female gender, age > 65 years, educational level < primary school, and income < US $4.00/day were significantly associated with reduced Ccr. Conclusion Chronic kidney disease prevalence in this population is similar to that seen in industrialized cuntries. If these figures are similar to those of the entire Mexican population, only out of 4 patients requring renal replacement therapy in the country currently has access to it.

14. Detection of early nephropathy in Mexican patients with type 2 diabetes

Cueto-Manzano AM, Cortes-Sanabria L, Martinez-Ramirez HR et al.

Kidney Int Suppl 2005 (97): S40-5.

Background The aims of this study were to determine the prevalence of early nephropathy in patients with type 2 diabetes mellitus (DM2) attending primary care medical units and to identify risk factors for nephropathy in this population. Method Seven hundred fifty-six patients with DM2 attending 3 primary care medical units were randomly selected. In a first interview, an albuminuria dipstick and a detailed clinical examination were performed, and a blood sample was obtained. If the albuminuria dipstick was positive, then a 24-hour urine collection was obtained within the next 2 weeks to quantify the albuminuria. In the blood sample, glucose, creatinine, and lipids were determined. Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation. Demographics and medical history were recorded from clinical examination and medical charts. Results Prevalence of early nephropathy (EN) was 40%, normal function (NF) was found in 38%, and overt nephropathy (ON) in 29%. Patients with more severe kidney damage were older (NF: 54 +/- 10; EN: 60 +/- 11; ON: 63 +/- 10 years, $P < 0.05$) and had a higher proportion of illiteracy (NF: 11%, EN: 17%; ON: 25%; $P < 0.05$). The more severe the nephropathy, the longer the median duration of DM2 (NF: 6.0; EN: 7.0; ON: 11.0 years; $P < 0.05$); the higher the frequency of hypertension (NF: 38; EN: 52%; ON: 68%; $P < 0.05$); and the higher systolic blood pressure (NF: 126 +/- 21; EN: 130 +/- 19; ON: 135 +/- 23 mm Hg; $P < 0.05$). Both nephropathy groups had a significantly higher proportion of family history of nephropathy (NF: 4%; EN: 9%; ON: 13%) and a higher frequency of cardiovascular disease (NF: 5%; EN: 12%; ON: 25%), whereas only patients with ON had peripheral neuropathy (NF: 21%; EN: 22%; ON: 43%) and retinopathy (NF: 12%; EN: 18%; ON: 42%) more frequently than others. Fasting glucose was poorly controlled in all groups (NF: 183 +/- 70; EN: 173 +/- 62; ON: 183 +/- 73 mg/dL). Large body mass index (NF: 29.3 +/- 5.3; EN: 29,7 +/- 5.6; ON: 29.6 +/- 5.5 kg/m(2), smoking (NF: 45%; EN: 43%; ON: 44%), and alcoholism (NF: 29%; EN: 29%; ON: 26%) were frequently found in this population, although there were no significant differences. In the multivariate analysis, only age, duration of DM2, and presence of retinopathy, hypertension, and cardiovascular disease were significantly associated with nephropathy. Conclusions Two thirds of Mexican patients with DM2 attending primary health care medical units had nephropathy, 40% of whom were at an early stage of the disease. Many modifiable and non-modifiable risk factors were present in these patients, but the most significant predictors for nephropathy are older age, longer duration of diabetes, and the presence of retinopathy, hypertension, and cardiovascular disease.

II. ETIOLOGY

1. Genetic and genomic approaches to glomerulosclerosis

Padiyar A, Sedor YR.

Curr Mol Med 2005 5 (5): 497-507.

Chronic kidney disease (CKD) is common, progressive and expansive to manage. Although modifiable risk factors can be treated and outcomes improved, CKD remains a chronic disease with excessive morbidity and mortality. The completion of the human genome sequence and the advent of methologies to define gene function provide new opportunities to manage and treat patients with CKD and other chronic diseases. Despite the lack of clear correspondence between genotype and phenotype and an obvious Mendelian inheritance pattern, CKD susceptibility has a genetic basis. In this review, we focus on recent studies of familial focal segmental glomerulosclerosis and the discoveries that have resulted from both genetic and genomic approaches used to understand its pathogenesis. Key slit diaphragm proteins were discovered using linkage analyses of the rare causes of glomerulosclerosis and subsequent work has characterized slit diaphragm function in health and disease. Podocyte dysfunction is now recognized as a key contributor to the functional and histologic derangements that characterize glomerular dysfunction in many common causes of CKD. In aggregate, these studies provide a paradigm for approaches to better define mechanisms of CKD and to identify novel therapeutic targets.

2. Molecular genetic approaches for studying the etiology of diabetic nephropathy

Ng DP, Krolewski AS.

Curr Mol Med 2005 5 (5): 509-25.

A critical challenge faced by clinical nephrologists today is the escalating number of patients developing end stage renal disease, a major proportion of which is attributed to diabetic nephropathy (DN). The need for new measures to prevent and treat this disease cannot be overemphasized. To this end, modern genetic approaches provide powerful tools to investigate the etiology of DN. Human studies have already estabilished the importance of genetc susceptibility for DN. Several major susceptibility loci have been identified using linkage studies. In addition, linkage studies in rodents have pinpointed promising chromosomal segments that influence renal traits. Besides augmenting our understanding of disease pathogenesis, these animal studies may facilitate the cloning of disease susceptibility genes in man through the identification of homologous regions that contribute to renal disease. In human diabetes, various genes have been evaluated for their risk contribution to DN. This widespread strategy has been propelled by our knowledge of the glucose-activated pathways underlying DN. Evidence has emerged that a true association does indeed exist for some candidate genes. Furthermore, the in vivo manipulation of gene expression has shown that these genes can modify features of DN in transgenic and knockout rodent models, thus corroborating the findings from human association studies. Still, the exact molecular mechanisms involving these genes remain to be elucidated. This formidable task may be accomplished by continuing to harness the synergy between human and experimental genetic approaches. In this respect, our review provides a first synthesis of the current literature to facilitate this challenging effort.

3. Carnosine as a protective factor in diabetic nephropathy. Association with a leucin repeat of the carnosinase gene CNDP1

Janssen B, Hohenadel D, Brinkkoetter P et al.

Diabetes 2005 (54): 2320-7.

The risk of diabetic nephropathy is partially genetically determined. Diabetic nephropathy is linked to a gene locus on chromosome 18q22.3-q23. We aimed to identify the causative gene on chromosome 18 to study the mechanism by which the product of this gene could be involved in the development of diabetic nephropathy. DNA polymorphisms were determined in 135 case (diabetic nephropathy) and 107 control (diabetes without nephropathy) subjects. The effect of carnosine on the production of extracellular matrix components and transforming growth factor-ß (TGF-ß) after exposure to 5 and 25 mmol/l D-glucose was studied in cultured human podocytes and mesangial cells, respectively. A trinucleotide repeat in exon 2 of the CNDP1 gene, coding for a leucine repeat in leader peptide of the carnosinase-1 precusor, was associated with nephropathy. The shortest allelic form (CNDP1 Mannheim) was more common in the absence of nephropathy (P = 0.0028, odds ratio 2.56 [95% CI 1.36 – 4.84]) and was associated with lower serum carnosinase levels. Carnosine inhibited the increased production of fibronectin and collagen type VI in podocytes and the increased production of TGF-ß in mesangial cells induced by 25 mmol/l glucose. Diabetic patients with the CNDP1 Mannheim variant are less susceptible for nephropathy. Carnosine protects against the adverse effects of high glucose levels on renal cells.

4. Characteristics of acute glomerulonephritis associated with human parvovirus B19 infection

Ieiri N, Hotta O, Taguma Y.

Clin Nephrol 2005 64 (4): 249-57.

Abstract Background Acute glomerulonephritis (AGN) is a rare complication of human parvovirus B19 (HPB19) infection. The clinical and pathological features of AGN associated with HPB19 (HPBAGN) have not yet been fully elucidated. Methods We analyzed 10 HPBAGN cases, focusing on their clinical and serological features. We also prformed histopathological examination of renal biopsy specimens obtained three of the 10 patients on day 15, 19, and 23, respectively, after the onset of symptoms. The phenotype of the glomerular infiltrating leukocytes in HPBANG was determined by immunohistochemical staining and compared with that og glomerular infiltrating leukocytes in poststreptococcal AGN (PSAGN) and lupus nephritis. Results The clinical course and laboratory data of the HPBAGN patients revealed female preponderance (male = 0, female = 10), erythema 9 of the 10 patients, leukopenia in 3, positive antinuclear antibody titer in 4, hypocomplementemia with low levels of C3, C4, and CH50 in 9, and liver dysfunction in 7. Endocapillary hypercellularity of leukocytes was demonstrated in all three patients who underwent renal biopsy. In comparison with PSAGN and lupus nephritis with crescents there were less neutrophil in HPBAGN compared to marked macrophage infiltrates that were equally intense in both control and the HPBAGN group. Conclusions

Our findings indicate that HPBAGN is characterized by female preponderance, erythema, lukopenia, positive antinuclear antibody titer, and hypocomplementemia, and that minor neutrophil infiltration may be related to mild clinical manifestations despite the marked fixation of glomerular

leukocytes in HPBAGN.

5. HIV-associated renal disorders: recent insights into pathogenesis and treatment

Berggren R, Batuman V.

Curr HIV/AIDS Rep 2005 2 (3): 109-15.

Renal electrolyte disorders, acute renal failure, and variety of chronic renal disease are common in IHV-infected patients. Glomerular disorders include IgA nephropathy, cryoglobulinemia, amyloidosis, and a lupus-like immune complex glomerulopathy. The most attention has been focused on collapsing glomerulopathy associated with nephrotic syndrome and progressive renal failure, which appears to be unique for patients with HIV/AIDS, called HIV-associated nephropathy (HIVAN), and it occurs predominantly in African-American patients. Investigations in humans and in a transgenic mouse model reveal direct infection of renal epithelial cells by HIV and toxic cellular and immunologic processes mediated by HIV glycoproteins as the principal pathophysiology of HIVAN. Highly active antiretroviral treatment may be associated with an improved renal outcome and even reversal of kidney disease in some patients. Treatment with angiotensin-converting enzyme inhibitors may avert progression of HIVAN to end-stage kidney disease and result in superior patients and kidney survival as compared with untreated patients.

6. Detection of enteroviruses in renal biosies from patients with immunoglobulin A nephropathy

Takashi A, Kawasaki Y, Yoshida K et al.

Pediatr Nephrol 2005 Aug 25 [Epub ahead of print]

Viruses have been suspected to be one of the causes of IgA nephropathy (IgAN). Recent studies have detected viruses in renal tissues of patients with IgAN. Enteroviruses have been reported as pathogenic agents in some renal diseases. We previously reported that group B coxsackieviruses cause pathological changes in experimentaly infected mouse kidney. The aim of the present study was to examine the participation of enteroviruses in the pathogenesis of renal diseases including IgAN. Renal biopsies of ten patients with IgAN (group 1) and of 19 patients with non-IgAN renal disease (group 2) were analyzed by polymerase chain reaction (PCR) for the presence of enteroviral RNA. Positive PCR results were obtained for three patients (30%) of group 1. We confirmed by sequencing that the positive PCR products were derived from strains of enteroviruses. One of these three patients also had a positive result for lymphocytes from peripheral blood. In contrast, enteroviral RNA was detected in none of the 19 patients of group 2. The incidence of enteroviral RNA detection in patients of group 1 was higher than that in group 2 ($P < 0.05$). Our findings suggest that enteroviral infection may have the possibility of becoming on of the factors involved in the mechanism of onset or evolution of IgAN.

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

Phillips J, Palmer A, Baliga R.

Pediatr Nephrol 2005 20 (10): 1494-5.

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 hare 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 organims 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 nephritogen strain and requires further investigation.

8. Crescentic glomerulonephritis associated with bacterial endocarditis – antibiotics alone may be sufficient. A case report

Manzoor K, Khan S, Ahmed E et al.

J Pak Med Assoc 2005 55 (8): 352-4.

Crescentic glomerulonephritis complcating the course of bacterial endocarditis carries a poor prognosis. Ideal treatment strategy is not clearly defined. In addition to antibiotic treatment, plasmapheresis and steroids have been used with variable results. Here we report a case of 40-year old was referred because of generalized body swelling and decrease urine output associated with low grade fever on and off for two to three months. She was diagnosed to have acute renal failure secondary to tricuspid valve endocarditis. Staphylococcus was isolated from blood culture and renal biopsy showed crescentic glomerulonephritis. She received dialysis support and antibiotics and had complete recovery of renal function 6 weeks after initiation of therapy. Eradication of infection with antibiotics treatment may be sufficient for resolution of crescentic glomerulonephritis associated with infective endocarditis in some cases.

9. Low birth weight, nephron number, and kidney disease

Luyckx VA, Brenner BM.

Kidney Int Suppl 2005 (97): 868-77.

More and more evidence is emerging that highlights the far-reaching consequences of prenatal (intrauterin) programming on organ function and adult disease. In humans, low birth weight (LBW) occurs more frequently in disadvantaged communities among whom there is often a disproportionately high incidence of adult cardiovascular disease, hypertension, diabetes mellitus, and kidney disease. Indeed, many epidemiologic studies have found an inverse association between LBW and higher blood pressures in infancy and childhood, and overt hypertension in adulthood. Multiple animal models have demonstrated the association of LBW with later hypertension, mediated, at least in part, by an associated congenital nephron deficit. Although no direct correlation has been shown between nephron number and birth weight in humans with hypertension, nephron number were found to be lower in adults with essential hypertension, and glomeruli tend to be larger in humans lower birth weight. An increase in glomerular size is consistent with hyperfiltration necessitated by a reduction in total filtration surface area, which suggest a congenital nephron deficit. Hyperfiltration manifests clinically as microalbuminuria and accelerated loss of renal function, the prevalence of which are higher among adults who had been of LBW. A kidney with a reduced nephron number has less renal reserve to adapt to dietary excess or to compensate for renal injury, as is highlighted in the setting of renal transplantation, where smaller kidney to recipient body-weight ratios are associated with poorer outcomes, independent of immunologic factors. Both hypertension and diabetes are leading causes of end-stage renal disease worldwide, and their incidence are increasing, essentially in underdeveloped communities. Perinatal programming of these 2 diseases, as well as of nephron number, may therefore have a synergistic impact on the development of hypertension and kidney disease in later life. Existing evidence suggest that birth weight should be used as surogate marker for future risk of adult disease. Although the ideal solution to minimize morbidity would be to eradicate LBW, until this panacea is realized, it is imperative to raise awareness of its prognostic implications and to focus special attention toward early modification of risk factors for cardiovascular and renal disease in individuals of LBW.

10. Microscopic polyangiitis after silicone breast implantation

Lyoda M, Ito J, Nagai H et al.

Clin Exp Nephrol 2005 9 (3): 252-4.

We describe the case of a patient who developed microscopic polyangiitis (MPA) after silicone breast implantation. A 60-year-old women who had undergone silicone breast implantation was admitted to our hospital with complaints of general malaise and hematoproteinuria. She was diagnosed as having MPA with evidence of acute progressive renal failure, pulmonary hemorrhage, and positivity for myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA). A renal biopsy showed severe necrotizing and crescentic glomerulonephritis with arteriolitis. The patient received high-dose steroids and plasma exchange treatment, but died of progressive pulmonary hemorrhage and multiple cerebral hemorrhage. Silicone implantation is associated with scleroderma, systemic lupus eythematosus, and rheumatoid arthritis. This case report indicate the possibility of the development of MPA after silicone breast implantation.

11. Oral contraceptives, angiotensin-dependent renal vasoconstriction, and risk of diabetic

nephropathy

Ahmed SB, Hovind P, Parving HH et al.

Diabetes Care 2005 28 (8): 1988-94.

Objective Diabetes, the leading cause of end-stage renal disease in the US, is belived to involve activation of the renin angiotensin system (RAS) as a risk factor for nephropathy. RAS activation occurs in healthy women oral contraceptives (OCs), but the effects of OC use on the diabetic kidney are unclear. Research design and methods Renal plasma flow (RPF) response to captopril, as an index of RAS activity, was investigated in 92 women (41 nondiabetic OC nonusers, 10 nondiabetic OC users, 29 diabetic OC nonusers, and 12 diabetic OC users). Based on the hemodynamic findings, we examined the impact of OC use on the development of nephropathy as a post hoc analysis in an inception cohort of 114 female patients with newly diagnosed type 1 diabetes followed for a median of 20.7 years (range 1-24). Results Nondiabetic OC nonusers showed minimal RPF vasodilator response to captopril (9 +/- 10 ml x min(-1) x 1.73m(2), P = 0.6). In comparison, nondiabetic OC users showed a significant increase (69 +/- 35 ml x min(-1) x 1.73 m (-2), P = 0.02) (P = 0.04 vs nondiabetic OC nonusers). Diabetic nonusers demonstrated the anticipated vasodilator response (58 +/- 12 ml x min(-1) x 1.73 m(-2), P < 0.0001). Diabetic OC users showed the largest responses (84 +/- 12 m x min(-1) x 1.72 m(-2), P = 0.002) (P = 0.04 vs diabetic nonusers). Plasma renin activity did not vary with OC use (P = 0.3). The RPF response to captopril and angiotensin receptor blocker were highly correlated (r = 0.72, P < o.001), suggesting clear involvement of the RAS. In the observational study, 18% (6/33 [95% CI 4.3-32.1]) of OC users developed microalbuminuria compared with 2% (2/81 [0-5.9]) of OC nonusers (P = 0.003, univariate analysis). After adjustment for known risk factors with a Cox regression model, OC use remained a predictor for the development of macroalbuminuria (relative risk 8.90 [95% CI 1.79-44.36], P = 0.008). Conclusion The strong association of OC use with angiotensin-dependent control of the renal circulation and development of microalbuminuria suggest that OC use may be a risk factor for diabetic nephropathy. Large prospective studies are required to further investigate this relationship.

12. Cyclosporine A induced epithelial-mesenchymal transition in human renal proximal tubular epithelial cells

McMorrow T, Gaffney MM, Slattery C et al.

Nephrol Dial Transplant 2005 (20): 2215-25.

Abstract Background Tubulointerstitial fibrosis is arelatively common and sinister complication of cyclosprine A (CsA) therapy that limits its use. CsA may have direst effects on renal tubular epithelial cells by promoting epithelial-mesenchymal transition (EMT). EMP plays an important role in embryonic development and tumourigenesis and has been described in organ remodelling during fibrogenesis. In this study, we investigated the effects of CsA on a human renal cell line as a model system to test the hypothesis that CsA can induce renal EMT. Methods Human renal proximal tubuler cell were treated with CsA (0.42-42 um) for periods up to 72h. Viability was

assessed by the Alamar Blue assay. Morphological changes were assessed by phase contrast microscopy. The effects on epithelial adherens molecule, ß-catenin and stress fibre protein. F-actin were analysed by indirect immunofluorescence. Reverse transcription-polymerase chain reaction was performed to measure the mRNA levels of extracellular matrix components. Expression of transforming growth factor-ß was measured by western blotting. Expression and activity of matrix metalloproteinases were measured by gelatin zymography. Results CsA induced striking morphological changes in epithelial cells, including changes in cellular morphology. F-actin stress fibre formation, delocalization of the adherens junction protein ß-catenin and increased levels of collagen IV and fibronectin. In addition, CsA-induced EMT was associated with increased TGF-ß1 protein levels and EMT was markedly attenuated in the presence of anti-TGF-ß1 antibody. CsA-induced EMT was also associated with increased expression of connective tissue growth factor (CTGF) suggesting that this molecule may be serve as downstream mediator of TGF-ß1 pro-fibrotic activity in this setting. Conclusions In aggregate, these data suggest that CsA is a direct stimulus fer EMT in renal tubule epithelial cells and implicate TGF-ß1 and CTGF as mediators of this response. The further delineation of the molecular components of this pro-fibrogenic response may suggest novel strategies through which to prevent CsA-induced tubulo-interstitial fibrosis in vivo.

13. Caspofungin is less nephrotoxic than amphotericin B in vitro and predominantly damages distal renal tubular cells

Wegner B, Baer P, Gauer S et al.

Nephrol Dial Transplant 2005 (20): 2071-9.

Abstract Background Caspofungin (CAS) has recently been approved for treatment of invasive aspergillosis. In clinical trials, CAS-induced nephrotoxicity was markedly less pronounced compared to amphotericin B (AmB). Nevertheless, in recent trial, nephrotoxicity in CAS-treated patients was considerably more pronounced than in preceding studies. Therefore, the aim of this study was to assess toxic effects of CAS on human renal proximal and distal tubular epithelial cells (PTC and DTC) in vitro, and to compare them to those of AmB. Methods Cells were isolated from human kidney tissue, and exposed to clinically relevant concentrations of CAS and AmB for 24h. Total DNA content and cell viability were determined by DAPI staining and modified MTT assay. For testing of cytotoxicity, LDH activity was measured in cell culture supernatants. To assess apoptotic effects, Annexin-binding assay and DAPI staining for detection of fragmented DNA were performed. Results DTC were more vulnerable towards the antifungal agents than PTC. In contrast to AmB, cell-damaging effects of CAS were less severe. DAPI staining revealed slight and dose-dependent antiproliferative effects of CAS at concentration reflecting relevant plasma levels. At these concentrations, cell viability, determined by MTT assay, was not decreased in PTC and DTC. LDH release was marginally increased in a dose-dependent manner; apoptosis was not detected. Nevertheless, at CAS concentrations reflecting potential tissue concentrations, cell damaging effects were considerably more pronounced. Conclusion Our results suggest that CAS in less nephrotoxic than AmB in vitro. The antiproliferative and cytotoxic effects of CAS predominantly affect DTC, which seem to be more susceptible to CAS induced damage.

14. Infliximab and nephrotic syndrome

Chin G, Luxton G, Harvey JM.

Nephrol Dial Transplant 2005 20 (12): 28246.

Abstract Infliximab is a chimeric tumor necrosis factor-alpha (TNF-alpha) monoclonal antibody, which has been used extensively in patients with rheumatoid arthritis and inflammatory bowel disease. It also appears to be effective in other conditions such as psoriasis and ankylosing spondylitis. The major side effect of infliximab is infection. Renal complications are uncommon and not well recognized. This report describes a probable case of infliximab-induced membranous nephropathy.

15. Renal involvement in bone marrow transplantation

Otani M, Shimojo H, Shiozawa S et al.

Nephrology (Carlton) 2005 10 (5): 530-6.

Bone marrow transplantation (BMT) is an effective therapeutic strategy for leukaemic malignancies and depressed bone marrow following cancer. However, its side effects on kidneys have been reported. Some drugs and irradiation are also suggested to be nephrotoxic. It is well known that haemolytic uremic syndrome (HUS) after BMT develops as late-onset BMT nephropathy. Cyclosporine A (CsA) is a possible cause. Radiation nephropathy shows changes that are similar to the histology of HUS. These findings suggest that endothelial damage is closely associated with the pathogenesis of post-BMT nephropathy. Recently, some patients have developed glomerulonephritis by graft-versus-host disease (GVHD) after BMT. In these patients immune deposits are found mainly subepithelium and mesangium equal to those of secondary membranous glomerulonephritis. A murine experimental model of GVHD manifests similar symptoms and histological changes to those of actual patients and may suggest the pathogenesis of glomerulonephritis.

16. „End-stage kidney'" in longstanding bulimia nervosa

Yasuhara D, Naruo T, Taguchi S et al.

Int J Eat Disord 2005 Oct 17 [Epub ahead of print]

Objective The extent of renal damage over long-term binge/purges has not been well documented in bulimia nervosa (BN). Method We describe a 52-year-old woman with long-standing BN subsequent to an 8-year history of anorexia nervosa (AN). Results: The patient showed chaotic binge/purges and chronic severe hypokalemia after recovery from AN at age 26 years, and renal

biopsy showed juxtaglomerular hyperplasia, which was diagnosed as pseudo-Batter's syndrome. Discussion Over the following 26 years, the patient's eating behaviors remained chaotic, and her renal function gradually deteriorated. After the patient died of pneumonia and sepsis age 52 years, autopsy of her kidney showed chronic interstitial nephritis, proximal tubular swelling, and diffuse glomerular sclerosis, suggesting chronic glomerular injury associated with long-term-term binge/purges, To our knowledge, this is the first case report of a patient with BN with long-term binge/purges who developed „end-stage kidney" characterized by hypokalemic nephropathy and diffuse glomerulosclerosis.

17. Fibrillary glomerulonephritis associated with monoclonal gammopathy of undetermined significance showing lambda-type Bence Jones protein

Nagao T, Okura T, Miyoshi K et al.

Clin Exp Nephrol 2005 9 (3): 247-51.

A 79-year-old woman was admitted to our hospital because of leg edema due to a nephrotic syndrome. Urinary and serum immunoelectrophoresis showed positive for the lambda type of Bence Jones protein. A bone marrow aspiartion test revealed mild plasmacytosis (6.4% of the total cells). These findings confirmed her diagnosis of monoclonal gammopathy of undetermined significance (MGUS). Her renal biopsy specimen revealed mild mesangial cell proliferation and an increase in the mesangial matrix. Immunufluorescence studies showed positive staining for IgG, IgA, C3 and kappa and lambda light chains in the capillary wall and mesangium area. Electron microscopy showed that the electron dense deposits in the thickened basement membrane were formed by randomly arranged 16- to 18nm nonbranching fibrills. A Congo red stain for amyloid was negative. Thes findings corresponded with the diagnosis of fibrillary glomerulonephritis. Therefore, this case showed a rare combination of fibrillary glomerulonephritis and MGUS.

18. Scleroderma with type III glomerulonephritis and MPO-ANCA antibodies in the serum

Herrera-Esparza R, Aquilar JR, Saucedo A et al.

J Eur Acad Dermatol Venerol 2005 19 (5): 617-20.

Scleroderma is an autoimmune disease characterized by early inflammatory infiltrates followed by fibrosis in the skin and internal organs. CREST is a relatively benign cutaneous variant of scleroderma that features clacinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and teleangiectases. Glomerulonephritis is a rare association of CREST. We are reporting a patient with CREST who developed glomerulonephritis and had anticentromere and antineutrophil cytoplasmic autoantibodies (ANCA) in her serum.

19. Nephrotic syndrome and renal failure after allogenic stem cell transplantation: novel molecular diagnostic tools for challenging differential diagnosis

Romagnani P, Lazzeri E, Mazzinghi B et al.

Am J Kidney Dis 2005 46 (3): 550-6.

Background Sudden onset of nephrotic syndrome after allogenic stem cell transplantation is rare and has been associated mostly with membranous glomerulonephritis related to chronic graft-versus-host disease (cGVHD). We report a case of nephrotic syndrome and rapidly progressive renal failure occuring in an young woman 3 years after stem cell transplantation from her HLA-identical brother. In the renal biopsy, a diffuse mononuclear cell infiltrate was observed. Furthermore, histological analysis, immunofluorescence, and electron microscopy of the kideny specimen defined the diagnosis as minimal change disease, a T-cell-mediated glomerulopathy associated with lymphoproliferative disorders, but that has never been described as an isolated manifestation of cGVHD. Methods The differential diagnosis was performed by using immunohistochemistry and laser capture microdissection combined with Taq-Man quantitative polymerase chain reaction. Results Infiltrating mononuclear cells in renal tissue consisted of T cells expressing DNA levels of an Y chromosome-specific gene quantitatively similar to those observed in a male subject, showing that these cells derived from the transplant donor and definitely excluding leukemia relapse. However, the large number of infiltrating T cells allowed the possibility that in this patient, minimal change disease could be related to an atypical from of GVHD. Conclusion This is the first study to use molecular techniques to show the differencial diagnosis of nephrotic syndrome after allogenic stem cell transplantation. This novel method approach might represent a key tool to characterize kidney infiltrate after allogenic stem cell transplantation.

20. IgA nephropathy in association with Crohn's disease

Forshaw MJ, Guirquis O, Hennigan TW.

Int J Colorectal Dis 2005 20 (5): 463-5.

Background Urological complications of inflammatory bowel diseses are seen in upto 25% of patients, but renal parenchymal disease is rarely reported. Case Report The authors describe a case of a 29-year-old man with clinical and radiological features of ileocaecoecal Crohn's disease. He had previously been investigated for painless macroscopic haematuria and a renal biopsy had revealed IgA nephropathy. Despite medical treatment, regular exacerbations of Crohn's disease were associated with deterioration in renal function and the development of hematuria. The patient eventually undrwent surgical resection of the terminal ileum and caecum. His renal disease has remained quiescent for the last 5 years following resection.

21. Complement and systemic lupus erythematosus

Karp DR.

Curr Opin Rheumatol 2005 17 (5): 538-42.

Purpose of review It is well recognized that th complement system plays multiple roles in systemic lupus erythematosus. Activation of the classical pathway by immune complexes leads to the generation of inflammatory mediators, thus promoting tissue injury. Complement activation also plays an importat role in the maintenance of tolerance to self-antigens. This review discusses recent insights in the role of complement in the pathogenesis of systemic lupus erythematosus. Recent Findings The antiphospholipid syndrome is a major feature of systematic lupus erythematosus. New findings have clearly demonstrated that the prothrombotic effects seen in a mouse model of this syndrome depend on complement activation, whereas the protective effects of heparin are due to its anticomplementary effects rather than its anticoagulant action. Secondly, a potential mechanism explaining the association of anti-C1q autoantibodies with lupus glomerulonephrits has been elucidated in a mouse model system. Summary New findings have helped to reinfoce the role of complement in the etiology and tissue damage of systemic lupus erythematosus. These findings point to more precise, mechanism-based therapies for autoimmune and inflammatory disease.

III. PATHOGENESIS

1. TLR agonists regulate PDGF-B production and cell proliferation through TGF-beta/type I IFN crosstalk

Chow EK, O'connel RM, Schilling S et al.

EMBO J 2005 24 (23): 4071-81.

Transforming growth factor-beta (TGF-beta) and type I interferon (IFN) autocrine/paracrine loops are recognized as key mediators of signaling cascades that control a variety of cellular functions. Here, we describe a novel mechanism by which Toll-like receptor (TLR) agonists utilize these two autocrine/paracrine loops differentially regulate the induction of PDGF-B, a growth factor implicated in a number of disease ranging from tumor metastasis to glomerulonephritis. We demonstrate that CpG-specific induction of PDGF-B requires activation of Smads through TGFbeta1 autocrine/paracrine signaling. In contrast, polyinosinic:polycytidylic acid strongly represses CpG's as well as its own intrinsic ability to induce PDGF-B mRNA through type I IFN-

mediated induction of Smad7, a negative regulator of Smad3/4. Furthermore, we have shown that this crosstalk mechanism translates into similar regulation of mesangial cell proliferation. Thus, our results demonstrate the importance of crosstalk between TGF-beta and type I IFNs in determining the specificity of TLR-mediated gene induction.

2. Immunolocalization of fibroblast growth factor-1 (FGF-1), its receptor (FGFR-1), and fibroblast-specific protein-1 (FSP-1) in inflammatory renal disease.

Rossini M, Cheunsuchon B, Donnert E et al.

Kidney Int 2005 68 (6): 2621-8.

Background The fibroblast growth factor (FGF) family has function in development, cell proliferation, migration, and differentiation. While FGF-2 induces fibrosis, the role of FGF-1 in inflammation and fibrosis is less defined. We examined the expression of FGF-1 and FGF receptor (FGFR-1) to determine if renal disease with warying etiologies of inflammation, including lupus nephritis (LN), acute interstitial nephritis (AIN) and acute rejection superimposed on chronic alloghraft nephropathy (CAN), showed varying patterns of expression. We also examined the expression of fibroblast-specific protein-1 (FSP-1), which has been linked to epithelial-mesenchymal transition (EMT) and fibrosis, to determine whether it was linked to potential profibrotic and inflammatory FGF-1 mechanisms. Methods Proliferative LN (PLN) (N=12), nonproliferative lupus nephritis (NPLN) (N=5), AIN (N=6), and normal kidneys (N=3) were studied. FGF, FGFR-1, and FSP-1 were localized by immunohistochemistry, and intensity scored on a 0 to 3+ scale. Double staining with CD68 and separate immunohistochemical staining for CD4 and CD8 with serial sections analysis were done to identify if T lymphocytes or macrophages showed staining for FGF-1 and FGFR-1 or FSP-1. Results In normal kidneys, FGF-1 was expressed in mesangial cells (0.67 +/- 0.58), glomerular endothelial (0.67 +/- 0.58), visceral, and parietal epithelial cells (1.67 +/- 0.58). FGFR-1 showed a similar pattern of staining but also was expressed in tubular epithelium, and arterial endothelium and smooth muscle. Expression of FGF-1 was increased over normal in glomerular parenchymal cells only in CAN in podocytes (2.30 +/- 0.58 vs. 3.00 +/- 0.00) ($P < 0.05$) and parietal epithelial cells (1.67 +/- 0.58 vs. 2.25 +/- 0.50) ($P < 0.05$). Infiltrating glomerular and interstitial inflammatory cells in diseased glomeruli also expressed FGF-1 and FGFR-1. Tubular cells expressed slightly increased FGFR-1 in renal diseases vs. normal, whereas tubules remained negative for FGF-1 in diseased kidneys. FSP-1 expression was prominent in the interstitium in all kidneys with interstitium in all kidneys with interstitial inflammation, and most prominent in CAN. Interstitial FSP-1 cells were consistent with a myofibroblast-type morphology, and did not stain with CD68. FSP-1 expression was closely associated with inflammatory cells expressing FGF-1 and FGFR-1. FSP-1 also showed positivity within crescent and occasional podocytes in PLN. Conclusion The expression of FGF-1 and FGFR-1 in infiltrating lymphocytes and macrophages, and of FGFR-1 in tubules, is supportive, but does not prove causality, of possibility that FGF-1 might have both autocrine and paracrine functions in renal inflammation. However, the initial stimulus for renal inflammation, whether immune complex, hypersensitivity or rejection, did not alter expression patterns of FGF-1 or its receptor. The colocalization of inflammatory infiltrates with interstitial fibrosis supports the possibility of a contribution of FGF-1 for chemotaxis and associated fibrosis, futher supported by interstitial FSP-1 expression closely associated with these inflammatory cells expressing FGF-1 and FGFR-1.

3. The sialoadhesin (CD169) expressing a macrophage subset in human proliferative glomerulonephritis

Ikezumi Y, Suzuki T, Hayafuji S et al.

Nephrol Dial Transplant 2005 20: 2704-13.

Abstract Background Sialoadhesin (Sn; CD169) is a lectin-like receptor whose expression is restricted to subsets of tissue and inflammatory macrophages. We have previously identified accumulation of SN+ macrophages as an important marker of disease progression versus remission in rat mesangial proliferative nephritis. The current study examined the significance of Sn+ macrophages in human proliferative glomeruloephritis. Methods Frozen kidney sections from normal adult human kidney (n=4) and pediatric nephropathy (n=40) were stained for total macrophages (CD68+ cells), Sn+ macrophages, CD3+ T-cells and collagen type I by immunofluorescence. Leukocyte infiltration and severity of glomerular lesions and interstitial damage were scored. A second protocol biopsy was performed in 27 cases and clinical and biopsy-based data obtained. Results Sn+ macrophages were absent from glomeruli in normal adult human kidney and in thin basement membrane disease (n=4), but were detected in 4 of 9 cases of purpura nephritis; 7 of 17 IgA nephropathy; 5 of 5 membranoproliferative glomerulonephritis, and 5 of 5 lupus nephritis. Sn+ macrophages were loclized in areas of focal glomerular and interstitial damage. Two-colour immunostaining confirmed that Sn+ cells are a subset of total CD68+ macrophages. The number of glomerular Sn+ macrophages correlated with the degree of proteinuria and glomerular lesions ($r = 0.44$, $P = 0.0045$ and $r = 0.82$, $P < 0.0001$; respectively), while interstitial Sn+ macrophages correlated with degree of proteinuria and intrstitial damage ($r = 0.59$, $P < 0.0001$ and $r = 0.75$, $P < 0.0001$; respectively). Combined immunostaining revealed that interstitial Sn+ macrophages and CD3+ T-cells co-localizated in areas of tubulointerstitial damage with increased type I collagen deposition. There was significant correlation between the number of interstitial Sn+ macrophages and CD3+ T-cells ($r = 0.74$, $P < 0.0001$). Most patients responded to a 2 year period of glucocorticoid therapy with a reduction in proteinuria and glomerular lesions and this correlated with the reduction in the number of glomerular Sn+ macrophages. Conclusion This study has identified Sn+ cells as a macrophage subset whose accumulation in the kideny correlates with proteinuria and histologic damage. These results, together with recent findings from animal studies, suggest that Sn+ macrophages may play an important role in progressive renal disease.

4. Protein gene product 9.5 and ubiqutin are expressed in metabolically active epithelial cells of normal and pathologic human kidney

Diomedi-Camassei F, Ravá L, Lerut E et al.

Nephrol Dial Transplant 2005 20: 2714-9.

Abstract Background In a study initially designed to evaluate the specific protein gene product 9.5 expression in parietal epithelial cells of Bowman's capsule, a marked positivity was also observed in the tubular and collecting duct epithelial cells. Since protein gene product 9.5 is an

important enzyme in the ubiquitin system proteolysis, and plays a regulatory role in cell cycle and prolifeartion, its presence in specific segments of the nephron was of considerable interest. Methods We investigated protein gene product 9.5 and ubiquitin expression in both normal and pathological renal samples (more than 100 cases) using an immunohistochemical technique. Results We found that protein gene product 9.5 and ubiquitin were constantly present in Bowman's capsule parietal cells and tubular/collecting duct epithelial cells, with the strongest positivity in metabolically active and proliferative conditions, such as tubular hypertrophy, cellular regeneration and crescent formation. Conversely, the expression of thes molecules was attenuated in atrophic tubules. Podocytes were negative. Conclusion The diffuse presence of the protein gene product 9.5 and ubiquitin in normal and pathologic metabolically active epithelial cells of the nephron suggest that these proteins (and likely the whole ubiqutin-proteasome complex) play a fundamental role in the mechanism upregulating protein metabolism of the kidney and that its expression is correlated with activated cellular functions, like proliferation.

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5. Apoptosis and proliferation in childhood acute proliferative glomerulonephritis

Ozaltin F, Besbas N, Bakkaloglu A et al.

Pediatr Nephrol 2005 20 (11): 1572-7.

Acute proliferative glomerulonephritis is characterized by glomerular hypercellularity that can be caused 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 the 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 were 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 normal renal function at follow-up; group 2 (n=8) were patients with end-stage renal failure or those who died. Immunohistochemical staining of proliferating cells (ki67) was done. In situ and labeling of DNA was used to evaluate apoptosis. Glomerular cell apoptosis was 45% in the patients with acute proliferative glomerulonephritis and 3% in controls ($p < 0.001$). apoptotic cells were identified in the tubulointerstitial compartment with higher and heavier immunostaining 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 0.31 +/- 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 glomeruilonephritis 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, $p =0.003$]. In conclusion, 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.

6. Pesistent familial hematuria in children and the locus for thin basement membrane nephropathy

Rana K, Wang YY, Powell H et al.

Pediatr Nephrol 2005 Oct 19 [Epub ahead of print]

This study examined how often children with persistent familial hematuria were from families where hematuria segregated with the known genetic locus for the condition known as benign hematuria or thin basement membrane nephropathy (TBMN) at COL4A3/COL4A4. Twenty-one unrelated children with persistent familial hematuria as well as their families were studied for segregation of hematuria with haplotypes at the COL4A3/COL4/A4 locus for benign familial hematuria and at the COL4A5 locus for X-linked Alport syndrome. Eight families (38%) had hematuria that segregated with COL4A3/COL4A4, and four (19%) had hematuria that segregated with COL4A5. At most, eight of the other nine families could be explained by disease at the COL4A3/COL4A4 locus if de novo mutations, non-penetrant hematuria or coincidental hematuria in unaffected family members was present individually or in combination. This study confirms that persistent familial hematuria is not always linked to Col4A3/COL4A4 (or COL4A5) and suggest the possibility of a further genetic locus for benign familial hematuria. Thsi study also highlights the risk of excluding X-linked Alport syndrome on the basis of the absence of a family history or of kidney failure.

7. Quantitative immunoelectron-microscopic analysis of the type IV collagen alpha1-6 chains in the glomerular basement membrane in childhood thin basement membrane disease

Akazawa H, Nakajima M, Nischiguchi M et al.

Clin Nephrol 2005 64 (5): 329-36.

Abstract Aim Thin basement membrane disease (TBMD) is characterized histologically by diffuse thinning of glomerular basement membrane (GBM). Although recent genetic analysis has shown that TBMD might be included within type IV collagen disorders, conventional immunohistochemical studies demonstrated normal labeling of type IV collagen alpha chains in the GBM. We have, however, successfully used confocal laser scanning microscopy to demonstrate a significantly reduced signal of type IV collagen alpha5 chain (alpha5(IV)) along capillary walls in TBMD. In order to further unerstand the association of type IV collagen with TBMD, we used immunoelectron microscopy to examine renal biopsies from 6 children with TBMD and six control children with minimal change nephrotic syndrome. Methods Ultrathin sections of LR gold resin were incubated with a rat monoclonal antibody against human alpha1(IV), alpha2(IV), alpha3(IV), alpha5(IV) or alpha6(IV) followed by colloidal gold conjugated goat anti-rat IgG. After taking electron micrographs, the labeling was quantitatively evaluated in the area occupied by the segments of basement membrane. The basement membrane was divided into three equal segments viz. subepithelial side, central portion and subendothelial side. Results In control subjects, the number of gold particles for alpha1(IV) or alpha2(IV) was significantly greater in the subendothelial side and central portion than in the subepithelial side of the GBM, whilst alpha3(IV), alpha4(IV) or

alpha5(IV) labeling was significantly more prominent in central portion compared to the subepithelial and subendothelial side of the GBM. TBMD samples showed a similar distribution pattern except that the subepithelial side and central portion of the GBM had a significantly reduced amount of alpha5(IV) antigen compared to control subjects. Conclusion This is the first report demonstrating a diminished labeling intensity of alpha5(IV) in the central portion and subepithelial side of the GBM in renal biopsy specimens from patients with TBMD. These findings suggest that an abnormality of alpha5(IV) might possible be associated with the pathogenesis of TBMD.

8. Molecular pathogenetic mechanisms of nephrotic edema: progression in understanding

Camici M.

Biomed Pharmacother 2005 (59): 215-23.

Abstract Molecular and pathogenetic mechanisms in sodium retention and water reabsorption of nephrotic edema are discussed. Are reported and analyzed molecular mechanisms about sodium retention in collecting dusct cells regarding activation and surface expression of epithelial sodium channels (EnaC) and sodium-potassium-ATPase (Na,K-ATPase) by aldosterone, natriuretic peptide system (underfill theory): is necessary a better understanding about the dysregulation of EnaC and Na,K-ATPase surface expression and the resistance to natriuretic peptide system. Are also reported and analyzed molecular mechanisms of sodium retention in proximal tubule cells regarding intrinsic albumin toxicity upon type 3 sodium-hydrogen exchanger ionic pump and the activity of sodium-hydrogen exchanger regulatory factor protein (overfill theory): a better knowledge about the link between albumin, sodium-hydrogen exchanger type 3 (NHE3) ionic pump, sodium-hydrogen exchanger regulatory factor protein is neccessary. Then molecular mechanisms of vasopressin free water retention through acquaporin water channels in collecting duct cells are discussed: further studies necessary to understand vasopressin release pathway (osmotic/nonosmotic) and V2 receptor activation with cell surface expression of renal acquaporins water channel.

9. Glomerulonephritis, Th1 and Th2: what's new?

Tipping PG, Kitching AR.

Clin Exp Immunol 2005 142 (2): 207-15.

Glomerulonephritis (GN), the major worldwide cause of chronic renal disease and renal failure, shows a wide spectrum of histological patterns, severity of injury and clinical outcomes that may be related to the nature of nephritogenic immune response. In the majority of cases, there is evidence of a central role for cognate immunity in the initiation of human GN and contributions of both humoral and cellular effector mechanisms have been demonstrated in both humans and in animal models. T helper cell subset are known to activate different immune effector mechanisms which influence disease outcomes in infectious and autoimmune diseases and evidence is now accumulating that Th1 and Th2 subsets direct diverging effector pathways that lead to different patterns and severity of

glomerular injury in GN. Th1-predominant responses appear to be associated strongly with proliferative and crescentic forms of GN that results in severe renal injury, while Th2 responses are associated with membranous patterns of injury. The challenge remains to understand fully the relevance of T helper cell subset responses to the spectrum of human GN and to apply this new knowledge to the development of more potent and selective therapeutic strategies.

10. Mechanisms of immune-deposit formation and the mediation of immune renal injury

Nangaku M, Couser WG.

Clin Exp Nephrol 2005 9 (3): 183-91.

The passive trapping of preformed immun complexes is responsible for some forms of glomerulonephritis that are associated with mesangial or subendothelial deposists. The biochemical characteristics of circulating antigens play important roles in determining the biologic activity of immune complexes in these cases. Examples of circulating immune complex disease include the classic acute and chronic serum sickness models in rabbits, and human lupus nephritis. Immune deposits also form „in situ". In situ immune deposits formation may occur at subepithelial, subendothelial, and mesangial sites. In situ immune-complexes formation has been most frequently studied in the Heyman nephritis models of membranous nephropathy with subepithelial immune deposits. While the autoantigenic target in Heyman nephritis has been identified as megalin, the pathogenic antigenic target in human membranous nephropathy had been unknown until the recent identification of neutral endopeptidase as one target. It is likely that there is no universal antigen in human membranous nephropathy. Immune complexes can damage glomerular structure by attracting circulating inflammatory cells or activating resident glomerular cells to release vasoactive substances, cytokines, and activators of coagulation. However, the principal mediator of immune complex-mediated glomerular injury is the complement system, especially C5b-9 membrane attack complex formation. C5b-9 inserts in sublytic quantities into the membranes of glomerular cells, where it produces cell activation, converting normal cells into resident inflammatory effector cells that cause injury. Excessive activation of the complement system is normally prevented by a series of circulating and cell-bound complement regulatory proteins. Genetic deficiencies or mutations of these proteins can lead to the spontaneous development of glomerular disease. The identification of specific antigens in human disease may lead to the development of fundamental therapies. Particularly promising future therapeutic approaches include selective immunosuppression and interferon in complement activation and C5b-9-mediated cell injury.

11. Cellular and molecular pathways that lead to progression and regression of renal fibrogenesis

Okada H, Kalluri R.

Curr Mol Med 2005 5 (5): 467-74.

Renal fibrosis is a common consequence and often a central feature of all the progressive renal

diseases that lead to end-stage renal failure. In comparison to wound healing, during kidney fibrosis the lenght of the post-inflammatory phase often exceeds and continues unchecked resulting in scar formation. Infiltrating immune cells and a heterogenous colony of interstitial cells derived from a variety of cellular origins such as resident mesenchymal cells, tubular epithelial cells, circulating fibrocytes, and bone marrow derived stem cells, communicate each other and with inflamed and surviving parenchymal cells via a network of cytokines and adhesion molecules to populate the renal tubulointerstitial space during early fibrogenesis. Such fibroblasts subsequently secrete abundant extracellular matrix to achieve architectural remodeling in parallel with functional deterioration. Renal fibrosis is a dominant determinant of the clinical outcome of patients and yet for the most part, current therapies are ineffective or only marginally effective. This review highlights recent advances in our understanding of the cellular and molecular events leading to the progression of renal fibrosis.

12. Upregulation of thymidine phosphorylase in chronic glomerulonephritis and its role in tubulointerstitial injury

Wang EH, Goh YB, Moon IS et al.

Nephron Clin Pract 2005 102 (3-4): c133-42.

Chronic tubulointerstitial injury (CTI), commonly a sequel to chronic glomerulonephritis (CGN), is associated with proliferation of new blood vessels. Angiogenesis is an essential process in chronic inflammation, and is controlled by a number of angiogenic factors including thymidine phosphorylase (TP). Knowledge of TP in renal disease is still rudimentary, and its role in CGN has not been explored. We analyzed the expression of TP by RTPCR, immunohistology and in situ hybridization in 20 human kidneys with CGN. To evaluate the degree of angiogenesis, we counted the microvessel density (MVD). MVD was significantly higher in all categories of CGN, between 19.7 +/- 7.7 and 58.9 +/- 7.5, compared to control value, 12.7 +/- 5.0 ($p< 0.05$). MVD was increased in areas of abundant mononuclear cell infiltration with minimal interstitial fibrosis, and decreased or absent in areas of marked fibrosis. There was a significant correlation between MVD and interstitial fibrosis ($p< 0.0001$). TP mRNA was upregulated for all categories of CGN. TP was strongyl expressed by mononuclear inflammatory cells and in most atrophic tubules. Each MVD and interstitial volume was significantly correlated with both the number of TP+ mononuclear cells and TP+ tubular cells, respectively ($p < 0.0001$). We have demonstrated an upregulation of TP and increase in MVD in areas of CTI in a variety of CGN. The up-regulation of tP may contribute to angiogenesis, which may play a critical role in the progression of interstitial fibrosis in CGN.

13. Insights into the mechanisms of renal fibrosis: is it possible to achieve regression?

Chatziantoniou C, Dussaule JC.

Am J Physiol Renal Physiol 2005 289 (2): F227-34.

Recent evidence suggest that the progression of renal fibrosis is a reversible process, at least in experimental models. The present review summarizes the new insights concerning the mechanisms of progression and regression of renal diseases and examines this novel evidence under the light of feasibility and transfer to human nephropathies. The involved mechanisms are discussed with particular emphasis on the fibrotic role of vasoactive peptides such as angiotensin II and endothelin and growth factors such as transforming growth factor (TGF)-beta. The possibility of regression is introduced by presenting the in vivo efficiency of antihypertensive treatments and of systems that antagonize the fibrinogenic action of TGF-beta such as bone morphogenic protein-7 and HGF. Finally, we provide a brief description of the promising future directions and clinical considerations about the applications of the experimental data to humans.

14. Hepatocyte growth factor is a downstream effector that mediates the antifibrotic action of peroxisome proliferator-activated receptor-gamma agonist

Li Y, Wen X, Spataro BC et al.

J Am Soc Nephrol 2005 Nov 16 [Epub ahead of print]

Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is a ligand-dependent transcription factor that plays an important role in the regulation of insulin sensitivity and lipid metabolism. Evidence shows that PPAR-gamma agonists also ameliorate renal fibrotic lesions in both diabetic nephropathy and nondiabetic chronic kidney disease. However, little is known about the mechanism underlying their antifibrotic action. This study demonstrated that PPAR-gamma agonists could exert their actions by inducing antifibrotic hepatocyte growth factor (HGF) expression. Incubation of mesangial cells with natural or synthetic PPAR-gamma agonists 15-deoxy-Delta(12,14)-prostaglandin J2 (15d-PGJ2) or troglitazone and ciglitazone suppressed TGF-beta-1-mediated alpha-smooth muscle actin, fibronectin, and plasminogen activator inhibitor-1 expression. PPAR-gamma agonists also induced HGF mRNA expression and protein secretion. Transfection studies revealed that 15d-PGJ2 stimulated HGF gene promoter activity, which was dependent on the presence of a novel peroxisome proliferator response element. Treatment of mesangial cells with 15d-PGJ2 induced the binding of PPAR-gamma to the peroxisome proliferator response element in the HGF promoter region. PPAR-gamma agonists also activated c-met receptor tyrosine phosphorylation, induced Smad transcriptional co-repressor TG-interacting factor expression, and blocked TGF-beta/Smad-mediated gene transcription in mesangial cells. Furthermore, ablation of c-met receptor through the LoxP-Cre system in mesangial cells abolished the antifibrotic effect of 15d-PGJ2. PPAR-gamma activation also induced HGF expression in renal interstitial fibroblasts and repressed TGF-beta1-mediated myofibroblast activation. Both HGF and 15d-PGJ2 attenuated Smad nuclear translocation in response to TGF-beta1 stimulation in renal fibroblasts. Together, these findings suggest that HGF may act as a downstream effector that mediates the antifibrotic action of PPAR-gamma agonists.

15. Methylenetetrahydrofolate reductase gene polymorphisms in essential hypertension relation with the development of hypertensive end-stage renal disease

Tylicki L, Fodinger M, Puttinger H et al.

Am J Hypertens 2005 18 (11): 1442-8.

Background The pathogenesis of hypertensive nephropathy is multifactoral and in addition to BP, other factors contribute to the development of this renal pathology and its progression to end-stage renal disease. These include genetic predisposition and increased pleasure level of homocysteine-intermediate protein catabolism product known to induce kidney injury. The 677C - -> T polymorphism in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene is associated with elevated homocysteine level in the general population, and therefore it has been hypothesized to be a risk factor for development of renal failure in the course of essential hypertension. Methods In this case-control, cross-sectional study the frequency of the MTHFR 677C - -> T and the 1298A - -> C polymorphism was compared between patients with hypertension-related chronic renal failure (N = 90), patients with essential hypertension without kidney injury (n = 90), and healthy individuals (n = 90) who were matched for age and gender. In addition, the influence of these polymorphisms on homocysteine concentration in individuals with essential hypertension was examined. Results The frequency of the MTHFR 677 TT genotype did not differ between groups (4.58%, 12.3%, and 11.1%, respectively). Patients with hypertension and the 677TT genotype showed significantly higher homocysteine levels as compared to individuals having CC and CT. In the multivariate correlation analysis the MTHFR 677TT genotype (P < .01; beta = 0.27), age (P < .001; beta = 0.33), and body mass index (P < .01; beta = 0.3) were indpendent predictors for total homocysteine level. Conclusion Plasma homocysteine levels in individuals with essential hypertension is affected by the MTHFR 677C - -> T polymorphism. However, we did not prove the hypothesis that MTHFR 677C - -> T influences the risk of development of renal failure in the course of hypertension.

16. Prostacyclin signaling in the kidney: implications for health and disease

Nasrallah R, Hebert RL.

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The balance between vasodilator and vasoconstrictor pathways is key to the maintenance of homeostasis and the outcome of disease. In the kidney, prostaglandins (PGs) uphold this balance and regulate renal function: hemodynamics, renin secretion, growth responses, tubular transport process, and cell fate. With the advent of cyclooxygenase (COX)-2-selective inhibitors, targeted deletions in mice (COX knockouts, PG receptor knockouts), and the discovery of intracrine signaling options for PGs (peroxisome proliferator-activated receptors and perinuclear PGE(2) receptors: EP (1,3,4), many advances have been made in the study of arachidonic acid metabolites. Although prostacyclin (PGI(2)) is a major product of the COX pathway, there is very little emphasis on its importance to the kidney. This review will discuss PGI(2) biology and its relevance to different aspects of renal disease (growth, fibrosis, apoptosis), highlighting the most significant research from the past decade of PGI(2) literature, what we have learned from other organ systems, while stressing the significance of cross talk between various PGI(2) signaling pathways and its implications for renal health and disease.

17. Puberty and chronic kidney disease

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Puberty is a period of dramatic physiologic changes when children become adults. Chronic kidney disease (CKD), like many disorders, may delay or blunt the onset and outcomes of puberty. These include attainment of adult height and reproductive capacity. Although nutrition and treatment effects may contribute to these phenomena, increasing evidence supports direct biological effects of CKD on the neurohypophyseal axis that controls these systems. Although CKD affects puberty, this life period also impacts the progression of CKD. Diabetes mellitus, posterior urethral valves, reflux nephropathy, and hypoplasia all appear to accelerate with sexual maturation. Potential mechanisms include increases in blood pressure and body size as well as altered endocrine physiology. Better understanding of the intercations of puberty and CKD may lead to better outcomes for children with CKD as well as longer preservation of native kidney function.

18. Class IV-S versus class IV-G lupus nephritis: clinical and morphologic differences suggesting different pathogenesis

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Background A recently proposed reclassification of lupus nephritis divides class IV (diffuse proliferative) lupus nephritis into those cases with predominantly segmental proliferative lesions (class IV-S) and those with predominantly global proliferative lesions (class IV-G). this report explores the validity of this distinction and possible differences in pathogenesis between the 2 types of lesions. Methods Patients from a previously reported series of severe lupus nephritis, with initial biopsies (Bx1) and control biopsies (Bx2) at months after induction therapy were reclassified according to the newly proposed classification. From the original series of 65 patients, 15 patients were reclassified as having class IV-S lesions and 31 patients class IV-G lesions. Clinical data at both biopsies and follow-up were available on all patients selected. Results Patients with IV-G lesions had worse proteinuria, lower serum hemoglobin, lower CH50s, and likely higher SCr (P= .06) and lower C3s (P= .08) than class IV-S patients. Serum CH50 and C3 correlated negatively with severity of class IV-G lesions, but not at all with class IV-S lesions. Patients with class IV-G lesions had greater overall immune deposits and subendothelial deposits on IF and greater hyaline deposits on light microscopy. By contrast, class IV-S showed predominant meangial deposists and a much higher rate of glomerular fibrinoid necroses (13.3 +/- 15.3% vs. 5.6 +/- 8.0% of viable glomeruli, P= .03). other distinctions included the fact that membranoproliferative features were found only in class IV-G lesions, and glomerular monocyte/macrophages were much more frequent in this froup than in class IV-S lesions (1.77 +/- 0.92 vs. 0.86 +/- 0.77, P= .008). Finally, class IV-G frequently involved all viable glomeruli (74.2% of cases), whereas segmental proliferative lesions never did (P < .0001). Survivals from doubling of SCr at 10 years did not differ between the 2 types at Bx1: 72.5% segmental versus 60.4% global, P= .53. However, among those with persistent lesions at Bx2

(11 IV-S and 9 IV.G), there was a dramatic difference in 10-year survival between IV-S lesions (63.6%) and IV-G lesions (0%), P= .08. Conclusion There ara definite clinical and morphologic differences between class IV-S and IV-G lesions. Data suggest that class IV-G lesions behave as an immune complex disease, having positive correlations with extent of immune deposits and negative correlation with serum complement levels, the model traditionally assumed for lupus nephritis as a whole. However, in class IV-S lesions, the presence of proportionally greater glomerular fibrinoid necroses and lack of correlation with extent of immune deposits suggest that these lesions may have a different pathogenesis.

19. Serological correlations with nephritis in systemic lupus erythematosus

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Abstract Autoantibodies have long been thought to participate in the pathogenesis of lupus nephritis. In this regard, antibodies to double stranded (ds)DNA and ribosomal P protein have been studied the most intensively. We now report a new specificity, antibodies to lipoprotein lipase (LPL) that is strongly associated with lupus nephritis and has a powerful synergistic effect with anti-ribosomal P antibodies in its association with nephritis. The recognition of anti-LPL antibodies and their synergy with anti-P-antibodies are discussed in terms of the pathogenesis of lupus nephritis.

20. Circulating anti-actin and anti-ATP synthase antibodies identify a sub-set of patients with idiopathic nephrotic syndrome

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Idiopathic nephrotic syndrome (iNS) with resistance or dependence to steroid is a comon disease in children but in spite of an increasing clinical impact its pathogenesis is unknown. We screened for the presence of circulating antibodies against glomerular (podocytes, mesangium) and tubular cells (tubular epithelia) a cohort of 60 children with iNS including 8 patients with a familial trait of iNS or with proven mutation of NPHS1-NPHS2 and 12 with good sensitivity to steroids. Positive sera were found in 8 cases, all belonging to the category without familial trait/molecular defects. The targets of antibodies were characterized with Western blot and MALDI-Mass utilizing beta-hexyl cell extracted separated with two-dimensional electrophoresis. In all cases antibodies of the IgM class directed against ATP synthase beta chain alone (4 cases) or combination with actin (3 cases); one child presented IgG against aldose reductase. The clinical picture was nephrotic syndrome with steroid resistance or dependence and variable cyclosporin sensitivity; 3 patients developed end stage renal failure. The basic pathology picture was focal segmental glomerulosclerosis (FSGS) in 4 cases

and mesangial proliferative glomerulonephritis with deposition of IgAM in 2. Overall, patients with circulating auto-antibodies could not be readely differentiated on clinical grounds with the exception of 3 children who developed positivity for antinuclear antibodies during the follow-up. Affinity-purified IgM from one patient who underwent plasmapheresis for therapeutical pourposes (but not from a normal pool) induced proteinuria in Sprague-Dawley rats and concomitant human IgM deposition within glomeruli. This is the first report of circulating anti-actin/ATP synthase beta chain antibodies in a subset of patients with iNS. Both pathological significance and clinical impact given by the presence of these antibodies and the relationship with other condition such as lupus-erythematosus, characterized by their prensence, must be defined.