

21. Podocyte involvement in human immune crescentic glomerulonephritis

Bariety J, Bruneval P, Meyrier A, et al.

Kidney Int 2005 68 (3): 1109-19.

Background The role of podocytes in human immune crescentic glomerulonephritis (GN) has been underestimated. This may be due to the confounding fact that „dysregulated” podocyte are able to proliferate, lose their markers, and acquire new epitopes. Moreover, in experimental anti-glomerular basement membrane (GBM) crescentic GN, podocytes participate in the crescent formation. The aim of this study was to investigate the involvement of podocytes in human immune crescentic GN. **Methods** Renal biosies from 12 patients with anti-GBM disease and 14 with class IV lupus GN were studied by immunohistochemistry for the following markers: (1) synaptopodin, GLEPP1, podocalyxin, podocin, alpha-actinin-4, and vimentin for podocyte identification; (2) PCNA, Ki-67, and p57 for cell cycle assessment; (3) cytokeratins for identifying epithelial cells but not normal podocytes; (4) CD68 for tagging a macrophagic epitope; (5) alpha-smooth-muscle-actin (alpha-SMA), a phenotypic marker of myofibroblasts. **Results** „True” (capsular) crescents lining Bowman’s capsule and (tuft) „pseudocrescents” covering the glomerular tuft with a persistent patent urinary space were present in the 2 types of crescentic GN in similar percentages. Several features indicated that podocytes were involved in the formation of the both crescent types. Identifiable podocytes expressed proliferation markers. Podocyte cytoplasmic expansion and racket-like podocytes bridged between the tuft and Bowman’s capsule. True and pseudocrescents conatined labeled podocytes. In addition, podocytes located outside of the crescent had often lost their markers (dedifferentiation) and acquired new epitopes (cytokeratins and CD68). **Conclusion** In human immune crescentic GN, podocytes undergo proliferation and dysregulation that are indicative of a podocytopathy. Podocytes contribute to crescent formation.

22. TRPC6 – new podocyte gene involved in focal segmental glomerulosclerosis

Kriz W.

Trends Mol Med 2005 Nov 10 [Epub ahead of print]

Hereditary kidney disease have long been an enigma with respect to the identity of the mutated genes and the mechanisms by which they develop. Recently, the podocyte has been identified as a primary target in both genetic and acquired glomerular disorders. Mutations discovered by Winn et al. And Reiser et al. in the gene encoding TRPC6, a non-selective cation channel of TRP family expressed in podocyte foot processes, have been shown to cause focal segmental glomerulosclerosis. It remains to be determined whether these mutations lead to (i) impaired channel function that initiates a new pathogenic mechanism or (II) decreased ability of the podocyte to adapt to normal pathophysiological challenges that account for disease development, as suggested for other late-onset autosomal-dominant podocyte diorders.

23. Is paraoxonase 192 gene polymorphism a risk factor for membranoproliferative glomerulonephritis in children?

Bilge I, Sirin A, Agachan B et al.

Cell Biochem Funct 2005 Sep 21 [Epub ahead of print]

We investigated the effects of paraoxonase (PON1) 192 polymorphism on serum PON1 activity and the impact of phenotypic expression on the risk and prognosis of Turkish children with membranoproliferative glomerulonephritis (MPGN). Eighteen children with biopsy-proven Type I MPGN (10 boys, 8 girls) and age-matched 53 healthy controls were included in the study. PCR (polymerase chain reaction), RFLP (restriction fragment length polymorphism) and agarose gel electrophoresis techniques were used to determine the PON1 192 genotype. PON1 activity was measured by spectrophotometric assay of p-nitrophenol production following addition of paraoxon. We found that PON1 192 genotype distribution (AA, AB, BB) in MPGN patients were 61.1%, 22.3% 16.8% and 15.1% in controls, respectively. The frequency of AA genotypes was significantly higher in the MPGN group (0.611) compared with the healthy controls (0.151) ($p < 0.001$). Although the serum PON1 activity was lower in MPGN patients (103.3 \pm 55.2 U/I) than the healthy controls (130.9 \pm 71.2 U/I), the difference was not statistically significant ($p = 0.0563$). In the genotypes of patients and controls classified according to PON1 A/B polymorphism; serum PON1 activities were significantly increased ($p < 0.001$, ANOVA) in the order of PON1 AA, AB and BB in both MPGN patients (82.4, 91.7 and 173.6 U/I) and healthy controls (85.9, 119.9 and 193.1 U/I), respectively. There was a significant relationship between the poor prognosis and having AA genotype and low PON1 activity. Of the 8 patients with poor prognosis, 7 had genotype AA and remaining one was AB heterozygote. Our results suggest that homozygosity for the A allele might have an important role on the risk for developing MPGN and may also be associated with the poor prognosis of disease. In conclusion, we suggest that the PON1 activities are affected by PON1 genetic variability in Turkish patients with MPGN.

24. Variations in the complement regulatory genes factor H (CFH) and factor H related 5 (CFHR5) are associated with membranoproliferative glomerulonephritis type II (Dense Deposit Disease)

Abrera-Abeleda MA, Nishimura C, Smith JL et al.

J Med Genet 2005 Nov 18 [Epub ahead of print]

Introduction Membranoproliferative glomerulonephritis type II or Dense Deposit Disease (MPGN II/DDD) causes chronic renal dysfunction that progress to end-stage renal disease in about half of patients within 10 years of diagnosis. Deficiency of and mutations in complement factor H (CFH) are associated with the development of MPGN II/DDD, suggesting that dysregulation of the alternative pathway of the complement cascade is important in disease pathophysiology. **Subjects** Patients with MPGN II/DDD were studied to determine whether specific allele variants of CFH and CFHR5 segregate preferentially with the MPGN II/DDD disease phenotype. The control group was comprised of 131 persons in whom age-related macular degeneration had been excluded. **Results** Indirect immunofluorescence using an anti-CFHR5 monoclonal antibody demonstrated

positive granular staining in renal biopsy from patients with MPGN II/DDD. Allele frequencies of four single nucleotide polymorphisms (SNPs) in CFH and three SNPs in CFHR5 were significantly different between MPGN II/DDD patients and controls. Conclusion Specific allele variants of CFH and CFHR5 are preferentially associated with the MPGN II/DDD disease phenotype. Determining how these allele variants affect regulation of alternative pathway of the complement cascade may lead to specific therapies to prevent and-stage renal failure in patients with this disease.

25. An interactive web database of factor H-associated hemolytic uremic syndrome mutations: insights into the structural consequences of disease-associated mutations

Saunders RE, Goodship TH, Zipfel PF et al.

Hum Mutat 2005 Nov 9 [Epub ahead of print]

Factor H (FH) is a central complement regulator comprised of 20 short complement repeat (SCR) domains. Nucleotide change within this gene (CFH) have been observed in patients with hemolytic uremic syndrome (HUS), and also membranoproliferative glomerulonephritis and age-related macular degeneration. All parts of FH are affected, but many mutations are clustered in the C-terminal part of FH. Up to now, structural analyses of HUS have been based on SCR-20, a domain that is involved in FH interacting with C3b, heparin, and endothelial cells. In order to identify the structural and functional consequence of HUS mutations, further disease-associated mutations were analyzed in terms of homology and nuclear magnetic resonance (NMR) models for factor H SCR domains. An interactive web database of 54 human HUS-associated mutations and others was created from the literature (www.FH-HUS.org). This has comprehensive search and analysis tools, integrating phenotypic and genetic data with structural analysis. Each mutation can be highlighted on the SCR structure together with the patients FH and C3 levels where available. Two new insights were obtained from our collection of data. First, phenotypic data on FH clarify our previously-proposed classification of Type I and Type II disorders that both lead to HUS, where Type I affects FH secretion and folding, and Type II leads to expressed protein in plasma that is functionally defective. Second, the new mutations show more clearly that SCR domains from SCR-16 to SCR-19 are important for the ligand binding activities of FH as well as SCR-20. This FH web database will facilitate the interpretation of new mutations and polymorphisms when these are identified in patients, and it will clarify the functional role of FH.

26. The glycans deficiencies of macromolecular IgA1 is a contributory factor of variable pathological phenotypes of IgA nephropathy

Xu LX, Yan Y, Zhang Y et al.

Clin Exp Immunol 2005 142 (3): 569-75.

Recent evidence has suggested that IgA1-containing macromolecules and the glycosylation of IgA1 in sera from patients with IgAN might involve the pathogenesis of IgAN. However, whether the

different histological phenotypes can be attributed or not to the aberrant glycosylation of macromolecular IgA1 has not yet been elucidated. The aim of the current study is to investigate the glycosylation of IgA1 molecules in serum IgA1-containing macromolecules and their association with pathological phenotypes of IgAN. Sera were collected from 40 patients with IgAN and 20 donors. Twenty patients had mild mesangial proliferative IgAN, the remaining 20 had focal proliferative sclerosing IgAN. Polyethylene glycol 6000 was used to precipitate the macromolecules from sera of patients and controls. Biotinylated lectins were used in an enzyme-linked immunosorbent assay (ELISA) to examine different glycans on IgA1 molecules. The α 2,6 sialic acid detected by elderberry bark lectin (SNA) and the exposure of terminal galactose (Gal) and N-acetylgalactosamine (GalNAc) were detected by *Arachis hypogaea* (PNA) and *Vicia villosa* lectin (VVL), respectively. The IgA1 glycan levels corrected by IgA1 concentrations were compared between patients and controls. Reduced terminal α 2,6 sialic acid of IgA1 (79.89 ± 25.17 versus 62.12 ± 24.50 , $P = 0.034$) was demonstrated only in precipitates from sera of patients with focal proliferative sclerosing IgAN, compared with those from controls. Reduced galactosylation of IgA1 molecules in precipitates was demonstrated in patients with both mild mesangial proliferative IgAN and focal proliferative sclerosing IgAN compared with normal controls (24.52 ± 18.71 versus 76.84 ± 32.59 , $P = 0.000$ and 33.48 ± 25.36 versus 76.84 ± 32.59 , $P = 0.000$). However, no significant difference was found in IgA1 glycosylation in the supernatant between patients and normal controls ($P > 0.05$). The glycosylation deficiency of IgA1 existed only in serum IgA1-containing macromolecules of patients with IgAN, and was associated with the renal pathological phenotypes. This suggests that aberrant glycosylation of IgA1 in serum macromolecules might be a contributory factor in the pathogenesis of IgAN.

27. FcγRIIa-131R allele and FcγRIIIa-176V/V genotype are risk factors for progression of IgA nephropathy

Tanaka Y, Suzuki Y, Tsuge T et al.

Nephrol Dial Transplant 2005 20 (11): 2439-45.

Background Fcγ receptors (FcγRs) may play an important role in positive and negative regulation of immune cell responses and immune complex (IC) clearance. Mesangial IgG deposition and circulating IgG/IgA-IC in sera are observed in patients with IgA nephropathy (IgAN). Therefore, the pathological roles of IgG-IC in IgAN have been discussed. On the other hand, several studies have identified FcγR polymorphisms (FcγRIIa, FcγRIIIa and FcγRIIIb) that determine susceptibility to autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis. The objective of the present study was to clarify whether FcγR polymorphisms influence susceptibility to IgAN, clinical features or severity in patients with IgAN. **Methods** Japanese patients with IgAN ($n = 124$) and healthy controls ($n = 100$) were genotyped for FcγR polymorphisms (FcγRIIa-131H or R, FcγRIIIa-176F or V and FcγRIIIb-NA1 or -NA2). The genotyping of these polymorphisms was performed using allele-specific polymerase chain reaction (PCR) methods. Associations among FcγR polymorphisms and susceptibility, age of onset, levels of serum immunoglobulins, intensity of glomerular IgG deposition and pathological severity were analysed. **Results** These three FcγR polymorphisms showed no significant difference in genotype and allele frequencies between the IgAN patients and healthy controls. Each FcγR polymorphism had no influence on age of onset, serum levels of IgG and glomerular IgG deposition in IgAN. However, FcγRIIa-131R (R/R or H/R) or FcγRIIIa-176V homozygous carriers (V/V) showed

significantly more severe injury than FcγRIIa-131H homozygous (H/H) ($P < 0.03$) or FcγRIIa-176F carriers (F/F or F/V) ($P < 0.03$), respectively. **Conclusion** The present study shows that polymorphisms of FcγRIIa and FcγRIIIa influence the severity of IgAN in Japan patients but not the incidence, suggesting that IgG-IC may play important roles in the progression and prognosis of this disease via FcγRs.

28. Dendritic cells of IgA nephropathy patients have an impaired capacity to induce IgA production in naive B cells

Eijgenraam JW, Woltman AM, Kamerling SW et al.

Kidney Int 2005 68 (4): 1604-12.

Background IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, characterized by mesangial IgA1 deposits. We have previously demonstrated that IgAN patients have a hampered IgA immune response after mucosal challenge with a neoantigen. Dendritic cells are critically involved in the initiation of humoral immune responses, not only via activation of T-helper cells, but also via direct effect on naive B cells. The aim of this study was to investigate the capacity of dendritic cells from IgAN patients to regulate IgA production. **Methods** Dendritic cells were generated by culturing monocytes for 7 days in the presence of interleukin (IL)-4 and granulocyte macrophage-colony-stimulating factor (GM-CSF). Dendritic cells from either IgAN patients (N= 12) or controls (N= 12) were cultured for 14 days with naive B cells in the presence of CD40L-transfected mouse fibroblasts (L-CD40L cells) and medium with or without IL-2 or IL-10. Supernatants were tested for the presence of immunoglobulins by specific enzyme-linked immunosorbent assay (ELISA). **Results** In the presence of CD40L and IL-10, dendritic cells were able to increase immunoglobulin production by naive B cells. Dendritic cells of IgAN patients induced significantly ($P = 0.026$) less IgA production than dendritic cells of control persons (2.30 μg/mL vs. 5.24 μg/mL), whereas no differences were found in the IgG and IgM production. When dendritic cells were replaced by supernatant of CD40L-stimulated dendritic cells of patients and controls, IgA production was increased, but no difference was seen between the two groups. **Conclusion** In the present study we show that dendritic cells of IgAN patients have an impaired capacity to induce IgA production in naive B cells, which might explain the observed IgA hyporesponse upon mucosal challenge with a neoantigen.

29. Peripheral B lymphocyte beta1, 3-galactosyltransferase and chaperone expression in immunoglobulin A nephropathy

Qin W, Zhou Q, Yang LC et al.

J Intern Med 2005 258 (5): 467-77.

Purpose Aberrant O-glycosylation of serum IgA(1) is presumed to be one of the main pathogenesis of immunoglobulin A nephropathy (IgAN). Beta1,3-galactosyltransferase (beta1,3GT), whose

activity requires coexistence of a specific chaperone, is the main enzyme which participate in the glycosylation process. The current study was carried out to elucidate the expression level of beta1,3GT (C1GALT1) and its chaperone (Cosmc) in IgAN, and their relationships with clinical features as well as IgA glycosylation level. Design, Setting and Subjects Forty-one patients with IgAN, 21 patients with non-IgAN glomerulonephritis and 26 normal controls included in the present study. Peripheral B lymphocytes were isolated, and then expression level of C1GALT1 and Cosmc were quantitatively measured by real-time reverse transcriptase polymerase chain reaction (RT-PCR). Serum IgA level and glycosylation level were determined by enzyme-linked immunosorbent assay (ELISA) and VV lectin-binding method. Correlation analysis was performed between C1GALT/Cosmc expression levels and clinical manifestations (severe proteinuria, renal dysfunction, gross hematuria). Results B-lymphocyte Cosmc gene expression level was significantly lower in IgAN patients than that of normal control and non-IgAN patients. ($P<0.05$), whilst no apparent disparity was observed in C1GALT1 expression level. Cosmc expression showed a negative correlation with IgA O-glycosylation level indicated by VV lectin-binding assay. Statistical analysis also indicated that the level of Cosmc expression was negatively correlated with severe proteinuria ($P<0.05$) instead of gross hematuria ($P>0.05$). Conclusion These data suggested that the aberrant IgA O-glycosylation in IgAN was regulated from a downregulation of beta1,3GT chaperone (Cosmc) expression in B lymphocyte, which is closely associated with clinical characteristics of the disease. This downregulation might be one of the fundamental pathogenic abnormalities in IgAN.

30. Up-regulation in the kidney and its genetic polymorphism of MUC20, a regulator of Met signaling cascade, in patients with IgA nephropathy

Narita I, Alchi B, Sato F et al.

Kidney Int 2005 68 (5): 1970-1.

MUC20, a novel mucin protein highly expressed in kidney, was isolated as an up-regulated gene in renal tissues of patients with IgA nephropathy (IgAN) [J Biol Chem 279:1968, 2004]. Functional analyses of MUC20 have demonstrated its role as a negative regulator of hepatocyte growth factor (HGF)-induced Grb2-Ras pathway. The C-terminus of MUC20 associated with the multifunctional docking site of Met, preventing Grb2 recruitment to Met and thus attenuating HGF-induced proliferation and matrix metalloproteinase expression (Mol Cell Biol 24: 7456, 2004). In addition, it has been suggested that the oligomerization of MUC20, caused by its overproduction or some other unknown factor(s), which leads to this association with Met. Interestingly, in human MUC20, the repeat numbers of the extracellular tandem domain, which may have an influence on the oligomerization, showed a divergence, with two to six repeat types in several human cell lines. In this study, to clarify the role of MUC20 in human kidney diseases, we analyzed the expression of MUC20 in kidney tissues of patients with IgAN by in situ hybridization. We also investigated the possible association of the tandem repeat polymorphism of MUC20 with renal survival in 236 patients with histologically proven IgAN. In normal kidneys, the expression of mUC20 was confined to the distal tubules, where Met was colocalized by immunohistochemistry. In addition, glomerular podocytes and the parietal epithelial cells lining Bowman's capsule demonstrated positive expression of MUC20. In renal tissues of IgAN, up-regulation of MUC20 expression in proximal tubules, as well as in distal tubules, was observed. By Kaplan-Meier analysis, the prognosis of IgAN patients with five or six of tandem repeat of MUC20 ($N=130$) was significantly better than those without ($N=106$, log-rank, $\chi^2(2) = 10.51$) ($P= 0.0012$). The tandem repeat

polymorphism of MUC20 was an independent risk factor for the progression of renal dysfunction after adjusting for other clinical risk factors, including hypertension, urinary protein excretion of more than 1.0 g/day, and no administration of renin angiotensin system inhibitors. This study supports the role of MUC20 in regulating the Met signaling cascade, which is implicated not only in renal development and maintenance of kidney function but also in tubular repair and regeneration under pathological conditions in human glomerulonephritis. The tandem repeat polymorphism in MUC20, which may directly affect its oligomerization and binding to Met, is associated with the renal prognosis of IgAN. Factors that regulate the function of MUC20 may be useful therapeutic agents for progression of renal injury.

31. Engagement of transferrin receptor by polymeric IgA1: evidence for a positive feedback loop involving increased receptor expression and mesangial cell proliferation in IgA nephropathy

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

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

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

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

Namikoshi T, Satoh M, Horike H et al.

Nephron Physiol 2005 102 (1): p9-16.

Background / Aims To determine the roles of peritubular capillary (PTC) loss and expression of vascular endothelial growth factor (VEGF) and its transcription factor, hypoxia-inducible factor-1 (HIF-1), in the progression of IgA nephropathy (IgAN), we analyzed the expression of VEGF and HIF-1, and the number of PTCs in patients with variable severity of IgAN. **Methods** Renal biopsy specimens from patients with IgAN (n = 23) were classified according to interstitial injury score: grade 0 (0%), grade 1 (1 – 25%), grade 2 (25 – 50%) and grade 3 (50 – 100%). We examined the immunohistochemical expression of CD34, VEGF and HIF-1alpha. **Results** VEGF was expressed in the cytoplasm of tubular epithelia, and VEGF-positive area significantly expanded in grades 1 (35.5 +/- 5.9%, mean +/- SD) and 2 (32.5 +/- 5.6%) compared with grade 0 (23.4 +/- 4.5%). The numbers of PTCs were significantly lower in grades 2 (559 +/- 49/mm(2)) and 3 (510 +/- 56/mm(2)) than grade 0 (708 +/- 49/mm(2)). HIF-1alpha was weakly expressed in tubular epithelia in grade 0, increased with progression to grade 2, and markedly decreased in grade 3. It was also increased in pericapsular interstitial area in grade 1. The expression pattern of HIF-1alpha did not parallel that of VEGF. In renal biopsies of 5 control patients with minor glomerular abnormality, glomerular expression levels of VEGF and HIF-1alpha were similar to those of IgAN grade 0 kidneys. **Conclusion** VEGF production was accelerated in the early stage of IgAN but it did not protect against PTC injury/loss. The lack of correlation between VEGF and HIF-1alpha expression suggest HIF-independent VEGF production in IgAN.

33. Genetic basis of diabetic nephropathy

Rincon-Choles H, Thameem F, Lehman DM et al.

Am J Ther 2005 12 (6): 555-61.

Diabetes mellitus is the leading cause of end-stage renal disease. Development and progression of diabetic nephropathy result from a combination of genetic susceptibility and metabolic and hemodynamic abnormalities. In America, some racial and ethnic minorities have a significant burden of diabetic nephropathy, and, although genetic studies suggest that inherited factors play a major role in the pathogenesis of diabetic nephropathy, little information has been gained on the genes and molecular mechanisms involved. The genetic background of diabetic nephropathy is believed to be polygenic, and the genes predisposing to the development and progression of diabetic nephropathy are actively being investigated. New knowledge in identifying and understanding the role of susceptibility gene(s) will provide valuable information that could help develop new preventive and therapeutic strategies.

34. Genetics of progressive renal failure in diabetic kidney disease

Liu Y, Freedman BI.

Kidney Int Suppl 2005 (99): S94-7.

Diabetic kidney disease is a microvascular complication that is observed in a minority of patients

with long-standing hyperglycemia. Diabetic nephropathy (DN) is associated with shortened patient survival, severe morbidity, and increased health care costs. Unfortunately, the incidence rates of DN continue to increase in Western societies, and DN is now the most common reported cause of end-stage renal disease in developed nations. DN results from complex interplay between inherited and environmental factors. This article reviews the data that support an inherited basis for susceptibility to DN by summarizing familial aggregation studies, genome-wide linkage, and population-based association analyses in diabetic and nondiabetic kidney disease. Recent evidence linking genes involved in the regulation of endothelial function with genetic predisposition to albuminuria is presented. The integration of carefully designed genetic linkage and association studies with gene expression experiments in human and animal models of diabetic kidney disease appear to offer great promise for detecting the molecular mechanisms underlying susceptibility to DN.

35. Assessing genetic susceptibility to diabetic nephropathy

Tanaka N, Babazono T.

Nephrology (Carlton) 2005 10 Suppl 2: S17-21.

Summary Diabetic nephropathy is a serious complication of diabetes and the leading cause of end-stage renal disease. Studies indicate both environmental and genetic factors contribute to the development and progression of diabetic nephropathy. In particular, epidemiological evidence shows a familial clustering of nephropathy in siblings with diabetes, supporting an important role of genetic susceptibility in the pathogenesis of diabetic nephropathy. A common approach in genetic research is assessment of candidate gene polymorphisms using case-control analysis; a number of studies have evaluated predictable candidate genes for diabetic nephropathy. In contrast, only a few studies have been used a whole genome approach, such as scanning of micro-satellite markers, in the assessment of genetic susceptibility to diabetic nephropathy. A whole genome linkage analysis using families of Pima Indians showed susceptibility loci for diabetic nephropathy on chromosome 3, 7, and 20. Another linkage analysis using discordant sib-pairs of Caucasian families with type 1 diabetes identified a critical area on chromosome 3q. However, these results have been inconclusive and further investigation is required. Recently, a genome-wide, case-control analysis identifying susceptibility genes for diabetic nephropathy was performed. As a result, a single nucleotide polymorphism in exon 23 of the solute carrier family 12 (sodium-chloride cotransporter) member 3 gene was found to be strongly associated with diabetic nephropathy. Although further assessment of this polymorphism is needed, this strategy offers great promise in the identification of genetic factors predisposing patients to diabetic nephropathy. Identification of genetic susceptibility markers may offer new hope in the diagnosis and treatment of diabetic nephropathy.

36. Genetics of diabetic nephropathy in type 2 DM: candidate gene analysis for the pathogenic role of inflammation

Lee SH, Lee TW, Ihm CG et al.

Nephrology (Carlton) 2005 10 Suppl 2: S32-6.

Summary Hypertension, poor glycemic control and albuminuria are well known risk factors for diabetic nephropathy, but these factors do not explain all of the inter-individual variabilities in the rate of progression to kidney failure. Recent evidence showed that genetic predisposition affected the hyperglycemia-induced nephrotoxicity in patients with type 2 diabetes mellitus (DM). We reviewed the present state of knowledge concerning the relationship between genetics and diabetic nephropathy in type 2 DM. However, the results are inconclusive and the genetic determinants of diabetic nephropathy are not fully understood. In addition, genetic background of nephropathy in type 2 DM was thought to be more complex than type 1 DM. Recent studies suggested that inflammation would be an essential component of type 2 DM and its complications. We postulated that increased systemic and/or intrarenal inflammation in high glucose milieu is important in the pathogenesis of nephropathy in patients with type 2 DM. To investigate the impact of inflammation on diabetic nephropathy, we studied several polymorphisms in genes encoding inflammatory cytokines and chemokine in patients with type 2 DM. Among them, -511 C/T in interleukin-1beta (IL-1beta), tandem repeat in IL-1 receptor antagonist (IL-1Ra), -308 G/A in tumour necrosis factor-alpha (TNF-alpha) were significantly associated with an increased risk of kidney failure. In addition, some of them were remarkably different from those previously reported in the NCBI or literature based on the western population. Our results suggest that inflammation could play a pathogenetic role in diabetic nephropathy in type 2 DN. A better understanding of genetic factors predisposing to diabetic nephropathy would not only help to identify diabetic patients at risk, but also helpful to unveil the pathogenesis of DN.

37. Assessment of 115 candidate genes for diabetic nephropathy by transmission/disequilibrium test

Ewens KG, George RA, Sharma K et al.

Diabetes 2005 54 (11): 3305-18.

Several lines of evidence, including familial aggregation, suggest that allelic variations contributes to risk of diabetic nephropathy. To assess the evidence for specific susceptibility genes, we used the transmission/disequilibrium test (TDT) to analyze 115 candidate genes for linkage and association with diabetic nephropathy. A comprehensive survey of this sort has not been undertaken before. Single nucleotide polymorphisms and simple tandem repeat polymorphisms located within 10 kb of the candidate genes were genotyped in a total of 72 type 1 diabetic families of European descent. All families had a least one offspring with diabetes and end-stage renal disease or proteinuria. As a consequence of the large number of statistical tests and modest P values, findings for some genes may be false-positives. Furthermore, the small sample size resulted in limited power, so the effects of some tested genes may not be detectable, even if they contribute to susceptibility. Nevertheless, nominally significant TDT results ($P < 0.05$) were obtained with polymorphisms in 20 genes, including 12 that have not been studied previously: aquaporin 1; B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene; catalase; glutathione peroxidase 1; IGF1; laminin alpha 4; laminin gamma 1; SMAD, mothers against DPP homolog 3; transforming growth factor, beta receptor II; transforming growth factor, beta receptor III; tissue inhibitor of metalloproteinase 3; and upstream transcription factor 1. In addition our results provide modest support for a number of candidate genes previously studied by others.

38. Polymorphisms in the gene encoding angiotensin I converting enzyme 2 and diabetic nephropathy

Frojdo S, Sjolind L, Parkkonen M et al.

Diabetologia 2005 Oct 7 [Epub ahead of print]

Aim / Hypothesis Substantial evidence exists for the involvement of the renin-angiotensin system (RAS) in diabetic nephropathy. Angiotensin I converting enzyme 2 (ACE2), a new component of the RAS, has been implicated in kidney disease, hypertension and cardiac function. Based on this, the aim of the present study was to evaluate whether variations in ACE2 are associated with diabetic nephropathy. Materials and Methods We used a cross-sectional, case-control study design to investigate 823 Finnish type 1 diabetic patients (365 with and 458 without nephropathy). Five single-nucleotide polymorphisms (SNPs) were genotyped using TaqMan technology. Haplotypes were estimated using PHASE software, and haplotype frequency differences were analysed using a chi(2)-test-based tool. Results None of the ACE2 polymorphisms was associated with diabetic nephropathy, and this finding was supported by the haplotype analysis. The ACE2 polymorphisms were not associated with blood pressure, BMI or HbA1c. Conclusion / Interpretation In Finnish diabetic patients, ACE2 polymorphisms are not associated with diabetic nephropathy or any studied risk factor for this complication. Further studies are necessary to assess a minor effect of ACE2.

39. The presence of allele D of angiotensin-converting enzyme polymorphism is associated with diabetic nephropathy in patients with less than 10 years duration of type 2 diabetes

Canani LH, Costa LA, Crispim D et al.

Diabet Med 2005 22 (9): 1167-72.

Aim To investigate the association between angiotensin-converting enzyme gene I/D polymorphism and diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (DM) taking into consideration the known duration of DM: Methods Cross-sectional study with 982 patients categorized according to urinary albumin excretion (UAE) into normoalbuminuria (UAE < 20 microg/min or < 17 mg/l, 24-h timed urine or spot random sterile urine, respectively), incipient DN (UAE 20-199 microg/min or 17-174 mg/l) and overt DN (UAE > 200 microg/min or > 174 mg/l or dialysis). Patients were further grouped regarding presence of the D allele (DD/ID) vs II) and DM duration (< or = 10 years or > 10 years). Results Incipient DN was diagnosed in 17.3% (n = 170), and 20.7% (n = 203) had overt DN (macroalbuminuria, n = 129; dialysis, n = 74). Genotype distribution (DD/ID/II) was similar in patients with incipient (49/92/29) or overt DN (77/89/37) if compared with patients without DN (181/308/120, P = 0.172). In patients with DM < or = 10 years, having the D allele (DD/ID) resulted in an odds ratio (OR) of 2.66 (95% CI: 1.12-6.58, P = 0.015) for incipient DN, and 3.19 (95% CI: 1.18-9.30, P = 0.012) for overt DN. In patients with longer DM duration, the D allele did not increase the risk for incipient (OR 0.68, 95% CI: 0.36-1.29, P = 0.206) or overt DN (OR 0.67 95% CI: 0.39-1.17, P = 0.138). Conclusion The DD/ID genotypes were associated with incipient or overt DN in patients with DM < or = 10 years.

40. Salt-sensitive blood pressure – an intermediate phenotype predisposing to diabetic nephropathy?

Strojek K, Nicod J, Ferrari P et al.

Nephrol Dial Transplant 2005 20: 2113-9.

Abstract Background Family studies point to important genetic determinants of diabetic nephropathy (DN). Blood pressure (BP) is higher in offspring of patients with type 2 diabetes and DN, but the pathomechanisms involved have not been elucidated. Methods We examined the salt sensitivity of BP after 5 days equilibration on a low (20mmol/day) vs high salt diet (220mmol/day) in three matched groups of 15 subjects each: (i) control individuals; (ii) offspring of type 2 diabetic parents without DN (DN-); and (iii) offspring of type 2 diabetic parents with DN (DN+). Ambulatory BP and hormones involved in sodium homeostasis [plasma renin activity (PRA), aldosterone and atrial natriuretic peptide (ANP)] as well as tetrahydrocortisol + 5-allotetrahydrocortisol/tetrahydrocortisone (THF+5 α THF)/THE ratio in the urine as an index of 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) activity analysed. Results In offspring of DN+ patients on a high salt diet, systolic and diastolic BP was 137/82 \pm 10/8 mmHg vs 125/77 \pm 12/8 mmHg in offspring of DN- patients ($p < 0.01$ for systolic BP). the salt-induced difference in mean BP between high and low salt diet was 5.2 \pm mmHg in offspring of DN+ patients vs 0.7 \pm 4.7 mmHg in offspring of DN- patients ($p < 0.002$). The proportion of 'salt-sensitive' individuals was 67% in offspring of DN+ patients vs 20% in offspring of DN- patients ($p < 0.05$). In all groups, a high salt diet caused a comparable decrease of PRA and p-aldosterone accompanied by an increase in ANP. The urinary (THF+5 α THF)/THE ratio was 1.23 \pm 0.36 in salt-sensitive individuals and 0.99 \pm 0.33 ($p < 0.03$) in salt-resistant subjects, consistent with increased activity of 11 β HSD2. Conclusion BP is more salt sensitive in offspring of type 2 diabetic patients with diabetic nephropathy. The salt sensitivity of BP may be an intermediate phenotype in individuals with a high risk of future diabetic nephropathy.

41. Mechanisms of high glucose-induced apoptosis and its relationship to diabetic complications

Allen DA, Yaqoob MM, Harwood SM.

J Nutr Biochem 2005 Sep 15 [Epub ahead of print]

Cellular response to high glucose are numerous and varied but ultimately results in functional changes and, often, cell death. High glucose induces oxidative and nitrosative stress in many cell types causing the generation of species such as superoxide, nitric oxide and peroxynitrite and their derivatives. The role of these species in high glucose-mediated apoptotic cell death is relevant to the complications of diabetes such as neuropathy, nephropathy and cardiovascular disease. High glucose causes activation of several proteins involved in apoptotic cell death, including members of the caspase and Bcl-2 families. These events and the relationship between high glucose-induced

oxidative stress and apoptosis are discussed here with reference to additional regulators of apoptosis such as the mitogen-activated protein kinase (MAPKs) and cell-cycle regulators.

42. High serum TNF-alpha level in Type 2 diabetic patients with microangiopathy is associated with eNOS down-regulation and apoptosis in endothelial cells

Makino N, Maeda T, Sugano M et al.

J Diabetes Complications 2005 19 (6): 347-55.

A high dose of tumor necrosis factor (TNF)-alpha induces endothelial dysfunction and enhances apoptosis in vitro. The present study was conducted to examine whether incubating human umbilical vein endothelial cells (HUVECs) with serum from Type 2 diabetic patients complicated with retinopathy and/or microalbuminuria demonstrate endothelial dysfunction. Serum levels of TNF-alpha and vascular endothelial growth factor (VEGF) were elevated in diabetic patients. Plasma levels of TNF-alpha, two soluble TNF-alpha receptors (sTNFR), and VEGF were assessed in diabetic patients (CD, n=21) complicated with retinopathy and/or nephropathy, uncomplicated diabetic patients (UD, n=18), and in healthy normal participants (ND, n=16). In HUVECs incubated with patient's serum, endothelial constitutive nitric oxide synthase (eNOS) protein expression were measured by Western blot analysis. Apoptosis in HUVECs was determined by optical microscopy, DNA fragmentation, and CPP32-like protease activity. Serum TNF-alpha, sTNFR-I, and asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NOS, in CD were significantly higher than in UD or NS. While, serum sTNFR-I and VEGF levels were significantly increased in the both diabetic patients, compared with those of NS, no difference was observed in the serum TNF-alpha, sTNFR-I, and ADMA levels between UD and NS. eNOS down-regulation and apoptosis were seen in HUVECs incubated with serum from CD for 24 h, but those observation were completely counteracted in the incubation by the addition of the antihuman TNF-alpha antibody. These results imply that eNOS down-regulation in CD is associated with high serum TNF-alpha levels despite of high serum of VEGF levels. Therefore, endothelial dysfunction in diabetic patients complicated with microangiopathy may, in part, be attributed to high serum TNF-alpha levels

43. Association between tumor necrosis factor-alpha G-308A polymorphism and risk of nephropathy in obese Chinese type 2 diabetic patients

Wang Y, Ng MCY, So WY et al.

Nephrol Dial Transplant 2005 20: 2733-8.

Abstract Background The G-308A polymorphism in the promoter region of the tumor necrosis factor alpha (TNF-alpha) gene has been reported to be associated with insulin resistance and obesity, both of which may increase the risk of diabetic nephropathy. We hypothesized that this polymorphism might interact with obesity to affect development of diabetic nephropathy. Methods

A consecutive cohort of 1281 Chinese type 2 diabetic patients enrolled for analysis. Genotyping of TNF-alpha G-308A polymorphism was performed using a PCR-based RFLP method with *NcoI* digestion. The mean value of the albumin creatinine ratio (ACR) of a random spot urine sample and a timed urinary collection was used to determine albuminuric status. Diabetic nephropathy was defined as serum creatinine > 150umol/L and/or mean ACR \geq 25mg/mmol. Obesity was defined as body mass index >25kg/m² using Asian criteria. **Results** The G-308A polymorphism was not associated with either obesity or nephropathy. Clinical characteristics were similar between GG and GA/AA genotype carriers. Amongst the obese patients, GG genotype carriers had a higher median (interquartile range) urinary ACR [3.16(0.70, 59.10) vs 1.28(0.48, 12.28)mg/mmol; $p = 0.01$] and albumin excretion rate [38.7(12.1, 620.3) vs 21.4(8.9, 224.0)ug/min, $p = 0.03$] than GA/AA carriers. On multiple logistic regression analysis, compared with non-obese GA/AA carriers, obese subjects with the GG genotype had a 2.5-fold increased risk (95% CI: 1.04-6.03; $P = 0.04$) of nephropathy after adjustment for confounding factors. Other independent factors for diabetic nephropathy included male sex, systolic blood pressure, triglycerides (logarithmically transformed value), and the presence of cardiovascular and microvascular complications. **Conclusion** Our findings suggest that the GG genotype of TNF-alpha G-308A polymorphism or a genetic variant in close linkage disequilibrium may interact with obesity to increase the risk of nephropathy in Chinese type 2 diabetic patients. Apart from the need for replication of these results, functional studies are required to clarify its significance.

44. Glomerular expression of thrombospondin-1, transforming growth factor beta and connective tissue growth factor at different stages of diabetic nephropathy and their interdependent roles in mesangial response to diabetic stimuli

Wahab NA, Schaefer L, Weston BS et al.

Diabetologia 2005 48 (12): 2650-60.

Aim/Hypothesis We quantified the glomerular expression of thrombospondin-1 (THBS1, also known as TSP-1), transforming growth factor beta 1 (TGFB1, also known as TGF-beta1) and connective growth factor (CTGF) at each stage of diabetic nephropathy. We also examined the roles of THBS1 and CTGF in mediating high-glucose- and glycated-albumin-induced synthesis of the matrix protein, fibronectin, by mesangial cells. **Methods** THBS1, latent and active TGFB1, and CTGF, were detected by immunohistochemistry and in situ hybridization in biopsies from 19 insulin-dependent diabetic patients with incipient, manifest and advanced diabetic nephropathy, and in 11 control kidneys. Findings were quantified by image analysis. Human mesangial cells were cultured with normal or high-glucose, albumin or glycated albumin (Amadori product), +/-THBS1 or CTGF antisense oligonucleotides, or with peptide W, an inhibitor of TGFB1 bioactivation by THBS1. proteins were measured by western blot analysis or ELISA. **Results** In glomeruli of normal kidneys, mRNA and protein levels for THBS1, latent-TGFB1 and CTGF were low. They were increased in the incipient stage of diabetic nephropathy, predominantly in mesangial areas, with further increases at later stages of the disease. Little or no active TGFB1 immunostaining was detected prior to manifest diabetic nephropathy. In contrast to high-glucose conditions, increases in fibronectin synthesis that were stimulated by glycated albumin were not dependent on THBS1 activation of latent TGFB1. However, increased fibronectin synthesis in both conditions required CTGF. **Conclusion/Interpretation** Increased glomerular expression of all three factors occurs from the earliest stage of diabetic nephropathy. In contrast to THBS, CTGF is required for mesangial synthesis of fibronectin stimulated by high glucose or glycated albumin, and is thus a potential

therapeutic target.

45. Podocyte hypertrophy in diabetic nephropathy

Kim NH.

Nephrology (Carlton) 2005 10 Suppl 2: S14-6.

Summary The development of irreversible renal changes in diabetes mellitus, such as glomerulosclerosis and tubulointerstitial fibrosis, are always preceded by early hypertrophic processes in the glomerular and tubular compartment. However, the role of hypertrophy of podocyte in the diabetic nephropathy have not been fully elucidated yet. Observation came from a cross sectional study in diabetic Pima Indians suggest that subjects with clinical nephropathy had fewer podocytes per glomerulus than those without nephropathy. Since podocytes are thought to be incapable of replications, this observation suggest that podocyte loss, or perhaps a low podocyte number per glomerulus, contributes to the development and progression of diabetic glomerulosclerosis. Podocyte hypertrophy caused by high glucose concentration leads to podocyte loss and is a new insight of pathogenesis of diabetic nephropathy; and it also provides us with new therapeutic strategies in diabetic nephropathy.

46. The human glomerular podocyte is a novel target for insulin action

Coward RJ, Welsh GI, Yang J et al.

Diabetes 2005 54 (11): 3095-102.

Microalbuminuria is significant both as the earliest stage of diabetic nephropathy and as an independent cardiovascular risk factor in nondiabetic subjects, in whom it is associated with insulin resistance. The link between disorders of cellular insulin metabolism and albuminuria has been elusive. Here, we report using novel conditionally immortalized human podocyte in vitro and human glomeruli ex vivo that the podocyte, the principal cell responsible for prevention of urinary protein loss, is insulin responsive and able to approximately double its glucose uptake within 15 min of insulin stimulation. Conditionally immortalized human glomerular endothelial cells do not respond to insulin, suggesting that insulin has a specific effects on the podocyte in the glomerular filtration barrier. The insulin response of the podocyte occurs via the facilitative glucose transporters GLUT1 and GLUT4, and this process is dependent on the filamentous actin cytoskeleton. Insulin responsiveness in this key structural component of the glomerular filtration barrier may have central relevance for understanding of diabetic nephropathy and for the association of albuminuria with states of insulin resistance.

47. Proteomics and diabetic nephropathy

Merchant ML, Klein JB.

Curr Diab Rep 2005 5 (6): 464-9.

Diabetes mellitus is acknowledged to be a group of metabolic diseases and heterogenous in natural history, pathogenesis, response to treatment, and disease progression and remission. Diabetic nephropathy (DN) accounts for approximately 40% of all newly diagnosed cases of end-stage renal disease. The complexity of diabetes and its complications requires a broad-based, unbiased, scientific approach such as proteomics. Recently, proteomics (the systematic analysis of protein identity, quantity, and function) has been applied to the study of DN. Proteomic investigations into diabetic kidney disease have identified new mechanisms of diabetic renal pathology, as well as potential urinary markers of DN. Other current proteomic advances in understanding DN include identifying the role of advanced glycation end products in decreased mitochondrial respiration and also the rapid development of mass spectrometric methods for protein and peptide markers of DN development and markers to pharmacological therapies. Proteomic analysis has only recently been applied to the study of DN, yet it has shown substantial potential.

48. Lipids and diabetic renal disease

Cooper ME, Jandeleit-Dahm KA.

Curr Diab Rep 2005 5 (6): 445-8.

Diabetic nephropathy is commonly associated with dyslipidemia, but the role of lipids in the progression of this disorders remains unresolved. In particular, the role of lipid-lowering drugs, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and fibrates, as renoprotective agents is not clarified. Experimental studies have demonstrated that dietary lipides promote renal injury and that statins, independent of their lipid-lowering effects, confer renoprotection via effects on intrarenal hemodynamics and renal cytokine and chemokine expression. Clinical studies have in general been underpowered, but a recent meta-analysis and findings from the Heart Protection Study suggest that statins may be renoprotective. Nevertheless, with the convincing antiatherosclerotic effects of these agents, including in the setting of diabetes, they should be widely administered in the diabetic population with or at risk for nephropathy.

49. Advanced glycation end products and the kidney

Bohlender JM, Franke S, Stein G et al.

Am J Physiol Renal Physiol 2005 289 (4): F645-59.

Advanced glycation end products (AGEs) are a heterogeneous group of protein and lipids to which sugar residues are covalently bound. AGE formation is increased in situations with hyperglycemia (e.g., diabetes mellitus) and is also stimulated by oxidative stress, for example in uremia. It appears that activation of the renin-angiotensin system may contribute to AGE formation through various mechanisms. Although AGEs could nonspecifically bind to basement membranes and modify their properties, they also induce specific cellular responses including the release of profibrogenic and proinflammatory cytokines by interacting with receptor for AGE (RAGE). However, additional receptors could bind AGEs, adding to the complexity of this system. The kidney is both: culprit and target of AGEs. A decrease in renal function increases circulating AGE concentrations by reduced clearance as well as increased formation. On the other hand, AGEs are involved in the structural changes of progressive nephropathies such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy. These effects are most prominent in diabetic nephropathy, but they also contribute to renal pathophysiology in other nondiabetic renal diseases. Interference with AGE formation has therapeutic potential for preventing the progression of chronic renal diseases, as shown from data of animal experiments and, more recently, the first clinical trials.

50. Advanced glycation end products and diabetic nephropathy

Thomas MC, Forbes JM, Cooper ME.

Am J Ther 2005 12 (6): 562-72.

Chronic hyperglycemia and oxidative stress in diabetes results in the formation and accumulation advanced glycation end products (AGEs). AGEs have a wide range of chemical, cellular, and tissue effects that contribute to the development of microvascular complications. In particular, AGEs appear to have a key role in the diabetic nephropathy. Their importance as downstream mediators of tissue injury in diabetic kidney disease is demonstrated by animal studies using inhibitors of advanced glycation to retard the development of nephropathy without directly influencing glycemic control. AGE modification of proteins may produces in changes charge, solubility, and conformation leading to molecular dysfunction as well as distributing interactions with other proteins. AGEs also interact with specific receptors and binding proteins to influence the renal expression of growth factors and cytokines, implicated in the progression of diabetic renal disease. The effects of AGEs appears to be synergistic with other pathogenic pathways in diabetes including oxidative stress, hypertension, and activation of the renin-angiotensin system. Each of these pathways may be activated by AGEs, and each may promote the formation of AGEs in the vicious cycle associated with progressive renal damage. It is likely that therapies that inhibit the formation of AGEs or remove established AGE modifications will form an important component part of future therapy in patients with diabetes, acting in concert with conventional approaches to prevent diabetic renal injury.

51. Pathogenic role of nitric oxide alterations in diabetic nephropathy

Prabhakar SS.

Curr Diab Rep 2005 5 (6): 449-54.

Diabetic nephropathy is the most frequent cause of terminal renal failure, requiring renal replacement therapy. Although a number of factors may contribute to the development of renal disease in diabetes, the recent past has witnessed an explosive growth in literature pertaining to the role of nitric oxide in diabetic nephropathy. However, there are significant controversies in the findings of these studies partly because of the complex metabolic pathways involved in the generation and fate of nitric oxide in the diabetic kidney. The following discussion presents a critical and balanced review of the current understanding of this subject.

52. Complement activation and diabetic vascular complications

Ostergaard J, Hansen TJK, Thiel S et al.

Clin Chim Acta 2005 361 (1-2): 10-9.

Diabetes mellitus is a major and increasing health problem worldwide. One of the most serious consequences of diabetes is the development of diabetic angiopathy, which includes cardiovascular disease, neuropathy, retinopathy and nephropathy. Diabetic nephropathy alone affects 15-25% of patients with type 1 diabetes and 30-40% of patients with type 2 diabetes and is the single-most important cause of end-stage renal failure in the Western World. Existing research has demonstrated the involvement of glycation factors, growth factors/cytokines, hemodynamic factors and intracellular changes in the pathogenesis of diabetic kidney disease. An emerging amount of recent data suggest that the complement system, especially the MBL pathway, plays an important role in the pathogenesis of diabetic vascular complications. Although the numerous therapeutic interventions available today may delay the development and progression of diabetes vascular complications, there is an ongoing need for new therapeutic strategies. In this article the evidence for a connection between the complement system and vascular dysfunction will be reviewed, with a special focus on the relation to diabetic kidney disease. Several ways of specifically manipulating the complement system already exist. However, whether or not these drugs provide new targets for intervention on diabetic vascular complications is still unknown.

53. Role of megalin, a proximal tubular endocytic receptor, in the pathogenesis of diabetic and metabolic syndrome-related nephropathies: protein metabolic overload hypothesis

Saito A, Takeda T, Hama H et al.

Nephrology (Carlton) 2005 10 Suppl 2: S26-31.

Summary Megalin is an endocytic receptor on the apical membranes of proximal tubule cells

(PTC) in the kidney, and is involved in the reabsorption and metabolism of various proteins that have been filtrated by glomeruli. Patients with diabetes, especially type 2 diabetes, or metabolic syndrome likely to have elevated serum levels of advanced glycation end products, liver-type fatty acid binding protein, angiotensin II, insulin and leptin, and renal metabolism and renal metabolism of these proteins is potentially overloaded. Some of these proteins are themselves nephrotoxic, while others are carriers of nephrotoxic molecules. Megalin is involved in the proximal tubular uptake of these proteins. We hypothesize that megalin-mediated metabolic overload in PTC leads to compensatory cellular hypertrophy and sustained Na(+) reabsorption, causing systemic hypertension and glomerular hyperfiltration via tubuloglomerular feedback, and named this as 'protein metabolic overload hypothesis'. Impaired metabolism of bioactive proteins such as angiotensin II and insulin in PTC may enhance hypertrophy of PTC and/or Na(+) reabsorption. Sleep apnoea syndrome, a frequent complication of diabetes and metabolic syndrome, may cause renal hypoxia and result in relative overload of protein metabolism in the kidneys. The development of strategies to identify patients with diabetes or metabolic syndrome who are at high risk for renal metabolic overload would allow intensive treatment of these patients in an effort to prevent the development of nephropathy. Further studies on the intracellular molecular signaling associated with megalin-mediated metabolic pathways may lead to the development of novel strategies for the treatment of nephropathy related to diabetes and metabolic syndrome.

54. Reactive oxygen species amplify glucose signalling in renal cells cultured under high glucose and in diabetic kidney

Ha H, Lee HB.

Nephrology (Carlton) 2005 10 Suppl 2: S7-10.

Summary Diabetic nephropathy is characterized by excessive accumulation of extracellular matrix (ECM) in the kidney. Reactive oxygen species (ROS) play a central role in the ECM synthesis and degradation in the glomeruli and tubulointerstitium leading to renal fibrosis. High glucose (HG) induces cellular ROS through protein kinase C (PKC)-dependent activation of NADPH oxidase and through mitochondrial metabolism. ROS thus generated active signal transduction cascade (PKC, mitogen-activated protein kinase, and janus kinase/signal transducers and activators of transcription) and transcription factors (nuclear-kappaB activated protein-1, and specificity protein-1), up-regulate transforming growth factor-beta1 (TGF-beta1), angiotensin II (Ang II), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1) gene and protein expression, and promote formation of advanced glycation end-product (AGE). PKC, TGF-beta1, AngII, and AGE also induce cellular ROS and signal through ROS leading to enhanced ECM synthesis. NF-kappaB – MCP-1 pathway is activated by ROS and promotes monocyte recruitment and profibrotic process in the kidney. HG- and TGF-beta1-induced PAI-1 up-regulation is mediated by ROS and contribute to ECM accumulation via suppression of plasmin activity. TGF-beta1-induced myofibroblast transformation of renal tubular epithelial cells (epithelial-mesenchymal transition) is also mediated by ROS and contribute to tubulointerstitial fibrosis. In summary, ROS transduce and amplify glucose signalling in renal cells under high glucose environment and play a critical role in excessive ECM deposition in the diabetic kidney. A better understanding of ROS production and removal will allow more effective therapeutic strategies in diabetic renal and other vascular complications.

55. Inhibition of MAP-kinase cascade normalizes the proliferation rate of fibroblasts from patients with type 1 diabetes and nephropathy

Maestroni A, Tentori F, Meregalli G et al.

J Diabetes Complications 2005 19 (5): 291-6.

Faster proliferation rate characterizes human skin fibroblast from patients with type 1 diabetes and nephropathy (DN), but the reason of this phenomenon is still unknown. Growth factor control cell proliferation through an intracellular mitogen-activated protein (MAP) kinase cascade. We have examined the effect of the inhibition of MAP kinase/ERK kinase, a key point of the MAP kinase cascade, on the proliferation rate of fibroblasts from 40 patients with type 1 diabetes (20 with and 20 without DN) and from 10 nondiabetic participants. Proliferation rate was measured by cell count in the presence or absence of 30 $\mu\text{mol/l}$ of MEK inhibitor PD 098059. In normal culturing conditions, proliferation rate was faster in fibroblasts from patients with DN ($0.175 \pm 0.009 \times 10^5$) cells (day⁻¹), mean \pm S.E.M.) than without DN (0.110 ± 0.009) and in nondiabetic participants (0.094 ± 0.008 ; ANOVA $P < 0.0001$). The inhibition of MEK induced a stronger reduction of proliferation rate in fibroblast from patients with ($0.079 \pm 0.006 \times 10^5$) cells day⁻¹; 55% of reduction) than without DN (0.068 ± 0.006 ; 38% of reduction) and in nondiabetic participants (0.064 ± 0.006 ; 32% of reduction), and differences among group were lost. In parallel, PD 098059 induced a greater reduction of MEK-dependent phosphorylation in lysates of fibroblasts from patients with (73%) than without (40%) DN. In conclusion, the inhibition of MEK normalizes the proliferation rate of fibroblasts from patients with DN, suggesting that the MAP kinase cascade could be involved in this cellular dysfunction.

56. Effects of insulin on methionine and homocysteine kinetics in type 2 diabetes with nephropathy

Tessari P, Coracina A, Kiwanuka E et al.

Diabetes 2005 54 (10): 2968-76.

Although hyperhomocysteinemia, an independent cardiovascular risk factor, is common in type 2 diabetes with nephropathy, the mechanism(s) of this alteration is not known. In healthy humans, hyperinsulinemia increases methionine transmethylation, homocysteine transsulfuration, and clearance. No such data exist in type 2 diabetes either in the fasting state or in response to hyperinsulinemia. To this purpose, seven male type 2 diabetic patients with albuminuria (1.2 ± 0.4 g/day, three with mild to moderate renal insufficiency) and seven matched control subjects were infused for 6 h 1-[methyl-(2)H(3), 1-(13)C]methionine. Methionine flux, transmethylation, and disposal into proteins as well as homocysteine remethylation, transsulfuration, and clearance were determined before and after euglycemic hyperinsulinemia (approximately 1.000 pmol/l). In type 2 diabetic subjects, homocysteine concentration was twofold greater ($P < 0.01$) and methionine transmethylation and homocysteine clearance lower (from approximately 15 to $>50\%$ and from approximately 40 to $>100\%$, respectively; $P < 0.05$) than in control subjects. The insulin-induced increments of methionine transmethylation, homocysteine transsulfuration, and clearance were

markedly reduced in type 2 diabetic subjects (by more than threefold, $P < 0.05$ or less vs. control subjects). In contrast, methionine methyl and carbon flux were not increased in the patients. In conclusion, pathways of homocysteine disposal are impaired in type 2 diabetes with nephropathy, both postabsorptive and insulin-stimulated states, possibly accounting for the hyperhomocysteinemia of this condition.

57. Plasminogen activator inhibitor-1 and diabetic nephropathy

Lee HB, Ha H.

Nephrology (Carlton 2005 10 Suppl 2: S11-3.

Summary Diabetic nephropathy is characterized by excessive accumulation of extracellular matrix (ECM) in the kidney. Decreased ECM degradation as well as increased ECM synthesis plays an important role in ECM remodeling that favours tissue fibrosis. Plasminogen activator (PA)/plasmin/PA inhibitor (PAI) system is involved in ECM degradation and PAI-1 plays a critical role in ECM remodeling in the kidney. Normal human kidneys do not express PAI-1 is overexpressed in pathologic condition associated with renal fibrosis including diabetic nephropathy. Reactive oxygen species mediate PAI-1 up-regulation in renal cells cultured high glucose, hypoxia, and TGF-beta. Recent studies utilizing PAI-1 deficient mice suggest that PAI-1 induce ECM deposition in diabetic kidney through increased ECM synthesis by TGF-beta1 up-regulation as well as through decreased ECM degradation by suppression of plasmin and MMP-2 activity.

58. From molecular footprints of disease to new therapeutic interventions in diabetic nephropathy: a detective story

Miyata T, Kurokawa K, van Ypersele de Strihou C.

Curr Drug Targets Immune Endocr Metabol Disord 2005 5 (3): 323-9.

Oxidative tissue damage in vivo is a complex phenomenon involving many factors and pathways. Proteins are particularly attractive targets for oxidative products analysis in order to understand better the physiopathology of human diseases. Protein modifications serve as footprints of biochemical processes. They also help ascertain the mechanism of anti-oxidative action of medical drugs and further search for novel agents that inhibit efficiently oxidative protein damage. Several drugs already used clinically interfere with oxidative protein damage through different mechanisms characteristic of their chemical structure. This review delineates the oxidative protein modifications existing in diabetic nephropathy and their regression in association with renoprotective anti-hypertensive agents. Our hypothetical approach will require further testing. Nevertheless, the insights gained on the biochemistry of protein modifications open new avenues towards the development of new classes of renoprotective agents for diabetic nephropathy.

59. Cilia and centrosomes: a unifying pathogenic concept for cystic kidney disease?

Hidebrandt F, Otto E.

Nat Rev Genet 2005 6 (12): 928-40.

Cystic kidney diseases are among the most frequent lethal genetic diseases. Positional cloning of novel cystic kidney disease genes that their products (cystoproteins) are expressed in sensory organelles called primary cilia, in basal bodies or in centrosomes. Primary cilia link mechanosensory, visual, osmotic, gustatory and other stimuli to mechanisms of cell-cycle control and epithelial cell polarity. The ciliary expression of cystoproteins explains why many other organs might be also affected in patients with cystic kidney disease. Protein-protein interactions among cystoproteins, and their strong evolutionary conservation, provide a basis for a multidisciplinary approach to unravelling the novel signaling mechanisms that are involved in this disease group.

IV. CLINICAL PRESENTATION

1. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden.

Evans M, Fryzek JP, Elinder CG et al.

Am J Kidney Dis 2005 46 (5): 863-70.

Background Mortality rates in patients with chronic renal failure (CRF) are high both before and after start of renal replacement therapy (RRT). However, few studies of mortality and progression have been performed in an unselected CRF population. **Methods** We followed up a population-based inception cohort of 920 men and women aged 18 to 74 years who had CRF (serum creatinine level > 3.4 mg/dL [>300 micromol/L] for men and >2.8 mg/dL [>250 micromol/L] for women) for 55 to 79 months. Relationships between the outcomes (death and start of RRT) and independent variables under study (age, sex, primary renal disease, body mass index [BMI], and glomerular filtration rate [GFR] at entry) were explored by using Cox regression models. **Results** Seven hundred thirty-nine patients (80%) started RRT during the follow-up period. As expected, GFR at entry was clearly linked to the incidence of RRT ($P < 0.0001$). Age was related inversely to incidence of RRT (adjusted relative risk for patients ≥ 65 years relative to patients < 45 years, 0.72; 95% confidence interval, 0.57 to 0.90). Men progressed to RRT more often than women

(adjusted relative risk, 1.59; confidence interval, 1.35 to 1.88). BMI unrelated to RRT incidence. By the end of follow-up, 389 patients with CRF (42%) had died, 89 them (10%) before the start of RRT. The most common primary cause of death was cardiovascular disease (37.5%).

Characteristics significantly related to a greater mortality rate included older age, diagnoses of diabetic nephropathy and nephrosclerosis, and low BMI. Conclusion Preuremic characteristics (age, sex, primary renal diagnosis, BMI, and GFR) are predictive of prognosis in unselected patients with CRF.

2. Correlates of systolic hypertension in patients with chronic kidney disease

Agarwal R, Andersen MJ.

Hypertension 2005 46: 514-20.

Abstract Hypertension in patients with chronic kidney disease (CKD) is predominantly systolic. The contribution of risk factors for hypertension to the overall systolic blood pressure (BP) is unknown. To study the relationship between risk factors for hypertension and systolic BP with CKD, 232 veterans (mean age 67 years; 96% men; 20% black; 39% with diabetes mellitus; estimated glomerular filtration rate [GFR] 48 ml/min/1.73m²) had clinic (routine and standardized measurements) and out-of-clinic (home and 24-hour ambulatory) BPs recorded. In multivariate analysis, using 17 risk factors, the log of the urine protein/creatinine ratio was the strongest predictor of systolic BP regardless of the BP measurement technique. The strength of the relationship between proteinuria and systolic BP was in the order ambulatory > home > standardized clinic > routine clinic BP measurement. Other independent predictors were age, race, and number of antihypertensive drugs used, and the model fit was better for out-of-clinic than clinic BP recordings. Estimated GFR was not an independent predictor of systolic BP by any technique. Nocturnal dipping was associated with higher estimated GFR, higher serum albumin, younger age, and less proteinuria. Proteinuria is the most important correlate of systolic BP in older men, the strongest relationship of which was with ambulatory and home systolic BP. Out-of-clinic BP recordings correlate better with target organ damage, as measured by proteinuria, and may be of greater clinical value than clinic BP recordings in predicting hypertension-related outcomes such as end-stage renal disease and death.

3. Significance of detecting urinary podocytes in patients with active glomerulonephritis

Li JZ, Huang HC, Liu Y.

Beijing Da Xue Xue Bao 2005 37 (5): 463-6.

Objective To establish a reliable method for detecting urinary podocytes, as a non-traumatic marker to evaluate glomerular injury in patients with glomerulonephritis. Methods Sixty patients with renal disease in our renal wards were diagnosed based on the pathological findings in their kidney biopsy tissues, which was examined by light microscopy, immunofluorescence and electron

microscopy. Sediments of morning urinary samples were collected and centrifuged onto glass slides before kidney biopsy. Thirtly healthy volunteers were enrolled as controls. The podocyte were identified by immunofluorescence staining by using monoclonal antibody against human podocalyxin (PCX) presenting on the surface of podocytes. The patients were divided in active inflammation group and chronic injury group according to their glomerular lesions. Results (1) The anti-human PCX antibody we used could specifically recognize the antigen expressed on podocytes in urine sediments examined by indirect immunofluorescence staining. (2) The PCX-positive staining cells in the urine were observed in various glomerulonephritis, and were absent in the healthy controls. (3) The rate of appearance of urinary podocytes was significantly higher in active inflammation froup compared with that in chronic injury group (72% vs 22.7%, $P<0.05$). (4) The glomerular injury index in the patients with PCX-positive staining cells in the urine was markedly increased than that in the patients with PCX-negative staining cells (154 +/- 60 vs 82 +/- 46, $P<0.05$). Conclusion The urinary podocytes could be detected in urine sediments from patients with glomerulonephritis by using anti-human PCX antibody, and this method may find further application in the markers to predict the activity of glomerular lesions.

4. Oxidative stress in children with kidney disease

Pavlova EL, Lilova MI, Savov VM.

Pediatr Nephrol 2005 20 (11): 1599-604.

The aim of this work was to study the dynamics of oxidative stress in the blood and urine of children with kidney diseases: glomerulonephritis (GN), pyelonephritis (PN), renal failure (RF), and lower urinary tract infections (LUTI). The concentration of conjugated dienes is increased in blood: GN 4 times and RF up to 2 times; and extremely increased in urine: GN 12 times and RF 4 times. The concentration of thiobarbituric acid reactive substances in urine shows a similar trend: GN 7 times, PN 2 times, and LUTI almost 3 times. Urine chemiluminescence is also increased: GN 5 times, PN and LUTI 3 times, and RF 6 times. Kidney disease leads to 2.5-fold inhibition of antioxidant catalase activity in blood and 10-fold in urine. Total antioxidant activity of urine is induced in all groups: GN 18 times, PN 2 times, RF 1.5 times, and almost 4 times in the LUTI group. Experimental data confirm that products of lipid peroxidation, intensity of chemiluminescence, and total and enzyme antioxidant capacity in combination with clinical parameters are a proper test for the dynamics of oxidative stress and markers of intoxication in children with inflammatory and immunological active parenchymal kidney disorders. These data could be helpful for the optimalization of complex and effective antioxidant therapy of children with kidney disease.

5. Combined top-down and bottom-up mass spectrometric approach to characterization of biomarkers for renal disease

Chalmers MJ, Mackay CL, Hendrickson CL et al.

Anal Chem 2005 77 (22): 7163-71.

Here we describe a mass spectrometry (MS) approach for biomarker discovery and structural characterization, based on both top-down and bottom-up analyses. Capillary electrophoresis (CE) coupled to electrospray ionization (ESI) time-of-flight (TOF) MS serves to separate and mass-measure the thousands of polypeptides contained in human urine. Statistical analysis of the differences between healthy control samples and patients with focal-segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, IgA nephropathy, and diabetic nephropathy validates multiple biomarkers for the control and each of the diseases. To identify those biomarkers, we employ preparative CE, enabling direct infusion ESI MS analysis, followed by sample manipulation and reanalysis where necessary. We show how tandem Fourier transform ion cyclotron resonance (FT-ICR) MS identifies these sometimes large (>8 kDa) biomarkers. Critically, we maintain connectivity between the CE TOF MS data and the ICR used for biomarker identification.

6. High serum C3 predicts poor outcome in IgM nephropathy

Myllymaki J, Saha H, Pasternack A et al.

Nephron Clin Pract 2005 102 (3-4): c122-7.

Background IgM nephropathy (IgMN) is an idiopathic glomerulonephritis with mesangial IgM deposition. The etiology of the deposition and possible association of serum and mesangial immunoglobulins and complement findings with renal outcome in IgMN unknown. Here we brought out data supplementary to our previous findings by reporting associations of immunological parameters with the outcome of IgMN. **Methods** Serum IgA, IgG, IgM, C3 and C4 were measured in 110 IgMN patients by single radial immunodiffusion or nephelometry. Mesangial IgA, IgG, IgM, C1q and C3 assessed in immunofluorescent study were graded as +/- . Seven histopathological parameters were semiquantitatively graded into three classes. The relationship of serum and mesangial immunoglobulin and complement findings with the clinical outcome and prognosis of IgMN was examined. **Results** We found significantly lower serum IgG and higher serum C3 levels in patients with nephrotic syndrome. Serum C3 correlated with the severity of glomerular histopathological changes. Of immunological parameters evaluated a low serum IgG/C3 ratio correlated best with the progression of renal disease. However, serum C3 was associated independently with progression in the case of patients without nephrotic syndrome. **Conclusion** In addition to previously reported factors, immunological parameters may also be helpful in determining the prognosis in IgMN. High serum C3 predicts poor outcome in IgMN, being associated with high-grade proteinuria, severe histopathological changes and progression.

7. Seasonal variation of lupus nephritis: high prevalence of class V lupus nephritis during the winter and spring

Schlesinger N, Schlesinger M, Seshan S.

Abstract Objective Systemic lupus erythematosus is a multisystem disease with many clinical variations, including renal involvement. Our aim was to whether lupus nephritis (LN) has a specific seasonality. Methods Reports of renal biopsies performed from 1990 to 2002 were reviewed. Three hundred and seventy-three patients with class II, III, IV, V LN were identified. Using the modified WHO classification of LN, diagnoses were tabulated and the seasonality (season of diagnosis) of LN was statistically analyzed. Results Class IV was detected in 179 patients (48%), class II in 63 patients (16.9%), class III in 73 patients (19.57%), and class V in 74 patients (19.9%). No difference could be detected in the number of patients diagnosed in each season when all 373 patients were analyzed as one group. The number of patients with class IV LN was higher during summer and fall than during the winter and spring. In contrast, a higher number of patients with class V LN were observed during the winter and spring season than during the summer and fall seasons. The percentage of patients with class V LN was significantly higher during winter and spring than during summer and fall. A similar, though non-significant, trend was seen for class III LN. A striking parallelism was found between the month of occurrence of class III and class V LN. The monthly distribution of the percentage of patients in each with class III and V LN showed a significant correlation. The monthly distribution of patients with class IV LN was different from those with either class III or V LN. Conclusion We found that the prevalence of class V LN was significantly higher than that of class III LN non-significantly higher in winter and spring. Parallelism between the monthly occurrences of class III and class V may suggest a common trigger. Analysis of the seasonality of LN may contribute to the understanding of the pathogenesis of LN, which may be multifactorial, as the different classes represent different types of glomerular injury. Further studies are needed to clarify this potentially important observation.

8. A case of elderly-onset systemic lupus erythematosus presenting as acute renal failure due to disseminated intravascular coagulation

Iyoda M, Matsumoto K, Hato T et al.

Clin Nephrol 2005 64 (4): 292-5.

Abstract herein we described a case of a patient with elderly-onset systemic lupus erythematosus presenting as acute renal failure due to disseminated intravascular coagulation. A 78-year-old man was admitted to our hospital with fever and generalized lymphadenopathy. He was diagnosed as having systemic lupus erythematosus on the basis of renal involvement, hematological abnormality and positivity for antinuclear and anti-double-stranded DNA antibodies. Renal biopsy revealed lupus nephritis (class III and V (A/C)) with focal glomerular thrombosis. He responded to hemodialysis and corticosteroid therapy with remission of serological values and renal function. Possible mechanisms underlying the coexistence of these conditions are discussed.

9. The clinical spectrum of primary renal vasculitis

Samarkos M, Loizou S, Vaiopoulos G et al.

Background and Objectives The vasculitides are potentially severe and often difficult to diagnose syndromes. Many forms of vasculitis may involve the kidneys. This review will focus on the clinical and histopathological aspects of renal involvement in the systemic vasculitis. **Methods** We searched the MEDLINE database using as key terms the MeSH terms and textwords for different forms of vasculitis and for renal involvement, creating a database of more than 2200 relevant references. **Results** The frequency of renal involvement in vasculitis varies among different syndromes. It is more frequent in Wegener's granulomatosis and microscopic polyarteritis, while it is uncommon to rare in other forms of vasculitis such as Behcet's disease and relapsing polychondritis. The vessels affected include the renal artery in Takayasu arteritis, medium-size renal parenchymal artery in classic polyarteritis nodosa, and glomerular involvement in Wegener's granulomatosis and microscopic polyarteritis. The clinical expression of renal vasculitis depends on the size of the affected vessels and includes renovascular hypertension, isolated nonnephrotic proteinuria, interstitial nephritis, and glomerulonephritis, which can be rapidly progressive. Diagnosis is established by a combination of history, clinical manifestations, laboratory findings (eg, urine sediment, urine protein, antineutrophil cytoplasmic antibodies), imaging techniques (renal angiography, especially when there is a suspicion of medium-to-large vessel disease, and chest radiograph), and finally, renal biopsy. Prognosis varies from unfavorable in rapidly progressive glomerulonephritis of microscopic polyarteritis, which can lead to renal failure, chronic dialysis, and renal transplantation, to benign, as in the case of Henoch Schonlein purpura, in which the majority of patients recover. **Conclusion** The manifestations and prognosis of renal vasculitis range widely. Renal involvement greatly influences prognosis and dictates the need for early and prompt immunosuppressive therapy. Thus, the clinician should be alert for the timely diagnosis and treatment of renal vasculitis.

10. Thrombotic thrombocytopenic purpura associated with polyarteritis nodosa.

Fujisaki K, Masutani K, Yoshimitsu T et al.

Clin Nephrol 2005 64 (4): 305-10.

Abstract We present a case of classical polyarteritis nodosa (PN) overlapping thrombotic thrombocytopenic purpura (TTP). A 70-year-old woman was transferred to our hospital because of general fatigue and fever. On admission, laboratory findings revealed leukocytosis, normochromic normocytic anemia and renal dysfunction. About one week later, she developed disturbance of consciousness, and laboratory findings revealed rapidly progressive thrombocytopenia and renal dysfunction. We suspected the presence of microscopic polyangiitis (MPA), based on mild elevation of myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibody (ANCA). On post-admission Day 11, renal biopsy was performed but the diagnosis of MPA could not be confirmed because of the absence of glomerular crescent formation or vasculitis. However, the biopsy specimen showed many collapsed glomeruli and interstitial inflammation, indicating the presence of occlusive lesions, such as vasculitis in larger arteries. We instituted methyl prednisolone pulse therapy, cyclophosphamide and plasma exchange, because the clinical symptoms also satisfied the criteria of TTP. Despite the intensive treatment, the patients died on 43rd day of hospitalization due to

thalamic hemorrhage. Autopsy showed typical findings of classical PN including disruption of arterial walls and fibrinoid necrosis in the medium-sized arteries of the kidneys and colon. We detected reduced activity of von Willebrand factor-cleaving protease (VWF-CP) and the presence of plasma inhibitory IgG against VWF-CP. A better understanding of the mechanisms would be useful.

11. Diabetes insipidus presentation before renal and pulmonary features in a patient with Wegener's granulomatosis

Duzgun N, Morris Y, Gullu S et al.

Rheumatol Int 2005 26 (1): 80-2.

We report a case of a 47-year-old woman with Wegener's granulomatosis complicated by central diabetes insipidus. The patient had initially seronegative polyarthrititis which mostly responded well to methotrexate and steroid therapy. Eight months later the patient suffered from polyuria and polydipsia. There were no abnormalities of the anterior pituitary hormones. Extensive evaluation of the patient revealed the presence of ANCA, in c-ANCA pattern and also PR3 positivity. Three months later findings of glomerulonephritis, as suggested by active urine sediment and gradual proteinuria, and, finally, asymptomatic pulmonary nodules completed the clinical picture of Wegener's disease within 1 year. Renal biopsy showed crescent formation in two glomeruli, consistent with ANCA-related glomerulonephritis which showed pauci-immun deposition by direct immunofluorescence. Diabetes insipidus symptoms mostly regressed; renal and pulmonary findings completely disappeared with glucocorticoid and pulse cyclophosphamide treatment. These findings show that diabetes insipidus may rarely develop early in the disease process and ANCA positivity was directly indicative of Wegener's granulomatosis before the classic clinical signs of the disease.

12. Goodpasture syndrome in a pregnant woman

Vasiliou DM, Maxwell C, Shah P et al.

Obstet Gynecol 2005 106 (5): 1196-9.

Background Goodpasture syndrome, an immunologic disorder characterized by glomerulonephritis and pulmonary hemorrhage, rarely presents pregnancy. **Case** We describe a patients who was diagnosed with Goodpasture syndrome in her second trimester. She required daily hemodialysis, intermittent plasmapheresis, and immunosuppressive therapy. Her pregnancy was complicated by hypertension, and she delivered a low birth weight neonate prematurely at 26 4/7 weeks of gestation by cesarean due to nonreassuring fetal status. Deterioration in the fetal status may have been secondary to complications of hypertension, in addition to prematurity. **Conclusion** Goodpasture syndrome in pregnancy may be associated with significant maternal and fetal morbidity.

13. A case of myeloperoxidase-antineutrophil cytoplasmic antibody positive-polyarteritis nodosa complicated by interstitial pneumonia and rapidly progressive renal failure

Sugimoto T, Kanasaki K, Koyama T et al.

Clin Rheumatol 2005 Dec 7 [Epub ahead of print]

A 73-year-old woman was admitted to our hospital because of persistent high fever and cough, generalized myalgia, and renal dysfunction. Laboratory examination revealed severe inflammatory signs, pulmonary fibrosis, progression of renal impairment with active nephritic urinary sediments, and a high titer of myeloperoxidase-antineutrophil cytoplasmic antibody, indicating that she might have microscopic polyangiitis with interstitial pneumonia and rapidly progressive glomerulonephritis. Her renal biopsy, however, showed tubulointerstitial changes with mild glomerular abnormalities, and renal angiography revealed that she had vascular lesions of medium-sized arteries, which were compatible with classical polyarteritis nodosa. Tissue biopsy of the clinically affected organ should be considered in anyone suspected to have vasculitis.

14. Persistent familial hematuria in children and the locus for thin basement membrane nephropathy

Rana K, Wang YY, Powell H et al.

Pediatr Nephrol 2005 20 (12): 1729-37.

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 familial 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/COL4A4 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 suggests the possibility of a further genetic locus for benign familial hematuria. This 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.

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

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

Since an active isoform of plasma hemopexin (Hx) has been proposed to be a potential effector molecule in minimal change disease (MCD), we tested plasma and urine samples from subjects with MCD in relapse ($n = 18$) or in remission ($n = 23$) (after treatment with prednisolone) for presence or activity of Hx. For comparison, plasma or urine from proteinuric subjects with focal and segmental glomerulosclerosis (FSGS), $n = 11$, membranoproliferative glomerulonephritis (MPGN, $n = 9$), IgA nephropathy ($n = 5$) or healthy control donors ($n = 10$), were incorporated into the study. Electrophoresis and Western blotting methods were used for evaluation of the Hx status, whereas protease activity of HX was tested upon kidney tissue in vitro according to standard methods. The results show (1) a decreased mean titer of plasma Hx exclusively in MCD relapse subjects as compared with MCD in remission (0.21 ± 0.14 mg/ml vs 0.44 ± 0.06 mg/ml; $p < 0.01$). Mean Hx titers in other proteinuric subjects ranged from 0.38 ± 0.05 mg/ml to 0.40 ± 0.06 mg/ml, whereas mean titer of healthy control was 0.59 ± 0.03 mg Hx/ml; (2) an increased Hx activity (expressed in arbitrary units) exclusively in plasma from MCD relapse subjects (3.3 ± 0.72 vs 1.16 ± 0.56 , MCD remission; $p < 0.01$); (3) different Western blot patterns in MCD relapse vs remission plasma; (4) reduced stainability or virtual absence of the 80-kD band in blots of urine from MCD relapse in contrast to urine samples from other proteinuric subjects with FSGS, MPGN, or IgA nephropathy. It is concluded that Hx in MCD relapse subjects may exist in an altered isoform, showing enhanced protease activity as compared with subjects in remission, subjects with other forms of primary glomerulopathy, or healthy control individuals.

16. Diagnosis and treatment of primary glomerular diseases membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy

Deegens JK, Wetzels JF.

Membranous nephropathy, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy are the most frequent and important primary glomerulopathies. Idiopathic membranous nephropathy and primary FSGS usually present with a nephrotic syndrome with or without renal insufficiency, whereas IgA nephropathy is more often characterized by (symptomless) hematuria and proteinuria. Although the outcome of these glomerulopathies is quite variable, many patients will progress to end-stage renal disease. In this review we discuss several aspects of the primary glomerulonephritis with emphasis on the potential benefit of specific immunosuppressive regimens.

17. Hepatitis C virus-associated glomerulonephritis without hepatitis C virus in the blood.

Yamabe H, Nakamura N, Nakamura M et al.

An 82-year-old woman with nephrotic syndrome and a 61-year-old woman with proteinuria and purpura on the lower extremities are reported. Both patients had test results positive for hepatitis C virus (HCV) antibody, but HCV RNA was not detected in the blood of either patient. The kidney biopsy showed membranoproliferative glomerulonephritis with capillary deposition of C3 and immunoglobulin M, indicating HCV-associated glomerulonephritis. These cases are suggestive to study the pathogenesis of this disease.

18. The IgA nephropathy Biobank. An important starting point for the genetic dissection of a complex trait

Schena FP, Cerullo G, Torres DD et al.

BMC Nephrol 2005 Dec 5 [Epub ahead of print]

Background IgA nephropathy (IgAN) or Berger's disease, is the most common glomerulonephritis in the world diagnosed in renal biopsied patients. The involvement of genetic factors in the pathogenesis of the IgAN is evidenced by ethnic and geographic variation in prevalence, familial clustering in isolated populations, familial aggregation and by the identification of a genetic linkage to locus IGAN1 mapped on 6q22-23. This study seems to imply a single major locus, but the hypothesis of multiple interacting loci or genetic heterogeneity cannot be ruled out. The organization of a multi-centre Biobank for the collection of biological samples and clinical data from IgAN patients and relatives is an important starting point for the identification of the disease susceptibility genes. **Description** The IgAN Consortium organized a Biobank, resulting IgAN patients and relatives following a common protocol. A website was constructed to allow scientific information to be shared between partners and to divulge obtained data (URL: <http://www.igan.net>). The electronic database, the core of the website includes data concerning the subjects enrolled. A search page gives open access to the database and allows groups of patients to be selected according to their clinical characteristics. DNA samples of IgAN patients and relatives belonging to 72 multiplex extended pedigrees were collected. Moreover, 159 trios (sons/daughters affected and healthy parents), 1068 patients with biopsy-proven IgAN and 1040 healthy subjects were included in the IgAN Consortium Biobank. Some valuable and statistically productive genetic studies have been launched within the 5th Framework Programme 1998-2002 of the European project No. QLG1-2000-00464 and preliminary data have been published in „Technology Marketplace” website:

<http://www.cordis.lu/marketplace>. **Conclusions** The first world IgAN Biobank with a readily accessible database has been constituted. The knowledge gained from the study of Mendelian diseases has shown that the genetic dissection of complex trait is more powerful when combined linked-based, association-based, and sequence-based approaches are performed. This Biobank continuously expanded contains a sample size of adequately matched IgAN patients and healthy subjects, extended multiplex pedigrees, parent-child trios, thus permitting the combined genetic approaches with collaborative studies.

19. Fibroblast-specific protein 1 is a specific prognostic marker for renal survival in patients with IgAN

Nishitani Y, Iwano M, Yamaguchi Y et al.

Kidney Int 2005 68 (3): 1078-85.

Background There is little direct evidence that fibroblast are involved in the progression of the renal interstitial fibrosis in human glomerulonephritis. With the availability of a new specific marker for fibroblasts, we determined the presence of fibroblasts in kidneys with IgA nephropathy (IgAN) and correlated their numbers with various clinical parameters. In particular, we also prospectively asked if the number of fibroblasts in the renal interstitium correlates with prognosis. **Methods** Cells positive for fibroblast-specific protein 1 (FSP1) were localized in renal biopsy specimens using immunohistochemistry with anti-FSP1 antibody. Clinical features were analyzed by one-way analysis of variance (ANOVA) with the Bonferroni correction. To assess the prognostic impact of the number of FSP1(+) fibroblasts on renal survival in 142 patients with normal serum creatinine, the relationship between covariates to renal survival were evaluated univariately using the long-rank test and multivariately using Cox proportional hazards. **Results** Fibroblasts identified by their expression of FSP1 accumulate in areas showing severe interstitial fibrosis. Some tubular epithelial cells undergoing epithelial-mesenchymal transition (EMT) in fibrotic areas also express FSP1. Numbers of FSP1(+) fibroblasts directly correlate with serum creatinine ($r = 0.74$, $P < 0.0001$) and inversely correlate with estimated creatinine clearance ($R = -0.54$, $P < 0.0001$), and by multivariate analysis, the clinical factors influencing renal survival are urinary protein excretion [≥ 1.0 g/day, relative risk (RR) = 4.20, $P = 0.032$], hypertension (RR 5.85, $P = 0.0027$), and ≥ 20 FSP1(+) fibroblasts per high power field (HPF) (RR 7.39, $P = 0.0015$). Staining for FSP1(+) fibroblasts is largely nonoverlapping with alpha-smooth muscle actin(+) (alpha-SMA) cells in the interstitium. **Conclusion** The target protein FSP1 identifies human fibroblasts and tubular epithelium undergoing EMT, and distinguished them from the diaspora of alpha-SMA(+) vascular smooth muscle cells. FSP1(+) fibroblasts are critically related to the progression of IgAN; consequently, staining FSP1 in renal biopsy specimens provides a valuable histologic index of progression.

20. Presentation, prognosis and outcome of IgA nephropathy in Indian adults.

Chacko B, John GT, Neelakantan N et al.

Nephrology (Carlton) 2005 10 (5): 496-503.

Background IgA nephropathy (IgAN) is not well characterized in India. This retrospective study of 478 patients with IgAN was performed to clarify the presenting features, prognostic factors and the renal survival rates of the disease. **Methods** Three hundred and forty-seven patients who had been followed on average for 27 months after diagnosis were divided into two groups based on renal function at diagnosis. In group 1 (229 patients), the creatinine clearance estimated by the Modification of Diet in Renal Disease formula was < 85 mL/min and in group 2 (118 patients) it was ≥ 85 mL/min. **Results** The predominant modes of presentation were nephrotic syndrome, hypertension and renal failure. Twenty-nine percent of patients had more than a 20% decline in renal function at the last follow up. Multivariate analyses with stepwise logistic regression identified hypertension (odds ratio (OR) 3.5), nephrotic range proteinuria (OR 3.4) and sclerosed glomeruli on biopsy (OR 4.1) to be independently associated with progression in group 1 and hypertension (OR 2.3) in group 2.

Seventeen percent of patients progressed to end-stage renal disease (ESRD). Using multivariate analysis by the Cox model, four risk factors for developing ESRD were identified: hypertension (hazard ratio (HR) 3.1); nephrotic proteinuria (HR 1.9); interstitial fibrosis (HR 2.5); and sclerosed glomeruli (HR 1.8). The renal survival rates at 1, 5 and 10 years were 84, 55 and 33%, respectively, with a median renal survival of 61 months from the time of biopsy. Conclusion The relatively rapid rate of progression of IgAN in India is suggestive towards a 'malignant' nature of the disease in this country.

21. C1Q nephropathy in children

Kersnik Levart T, Kenda RB, Avgustin Cavic M et al.

Pediatr Nephrol 2005 20 (12): 1756-61.

C1q nephropathy (C1qNP) is a peculiar form of glomerulonephritis characterized by mesangial immunoglobulin and complement deposits, predominantly C1q, with no evidence of systemic lupus erythematosus. We describe the incidence, manifestation, histopathologic findings, follow-up, treatment and outcome of C1qNP. Twelve C1qNP patients were identified among 131 children who had undergone renal biopsy, accounting for a 9.16% incidence of C1qNP. Light microscopy examination showed focal segmental glomerulosclerosis (FSGS) with or without diffuse mesangial proliferation (n=6), minimal change disease (MCD) (n=4) or focal glomerulonephritis (n=2). C1q deposits were found in all, while electron microscopy visible deposits in nine cases. Eight children presented with nephrotic syndrome, while one had nephrotic proteinuria and renal insufficiency that progressed to end-stage renal failure. The remaining three patients presented with non-nephrotic proteinuria associated with microhematuria, hypertension or renal insufficiency. Only one nephrotic syndrome patient responded excellently to corticosteroids, while four became corticosteroid dependent, and three were corticoid resistant, showing a very poor response to other immunosuppressive therapy as well. Patients with non-nephrotic proteinuria demonstrated fixed laboratory findings. Most C1qNP patients had FSGS or MCD, the majority of them presenting with corticosteroid-dependent or corticosteroid-resistant nephrotic syndrome. The latter showed a very poor response to any immunosuppressive therapy and high risk for progressive renal insufficiency.

22. C1q nephropathy with asymptomatic urine abnormalities

Nishida M, Kawakatsu H, Okumura Y et al.

Pediatr Nephrol 2005 20 (11): 1669-70.

We found four cases of C1q nephropathy (C1qN) among a total of 193 pediatric series of first renal biopsies. Among them, 94 biopsies were performed because of asymptomatic urine abnormalities

detected by school urinary screening program in Japan; three cases out of these 94 biopsies (3.2%) met the criteria of C1qN. One case out of the remaining 99 biopsies with symptomatic renal diseases (1%) also met the criteria of C1qN. Three cases with asymptomatic onset presenting with mild proteinuria with or without hematuria equally showed histologic features of membranoproliferative glomerulonephritis and showed improvements in urinalysis without corticosteroid treatment. Our data suggest that membranoproliferative glomerulonephritis may be a common histological feature of asymptomatic pediatric C1qN in Japan and that this type of glomerulopathy may follow a relative good clinical course without steroid therapy.

23. Prediction, progression and prevention of diabetic nephropathy. The Minkowski Lecture 2005.

Rossing P.

Diabetologia 2005 Dec 9 [Epub ahead of print]

Diabetic nephropathy is a major problem for patients and health care system. The costs of treatment remain high. To confront the ongoing challenge, we need to identify individuals at high risk for initiation and progression of this devastating complication. Risk factors include genetic markers; constitutional factors such as low birthweight; hemodynamic factors, including activation of the RAS system and hypertension; metabolic factors such as glycaemia; and additional factors such as urinary AER and smoking. Modifiable risk factors should be treated aggressively. Potential new markers of risk include indices of increased inflammation, changes in coagulation, endothelial dysfunction, growth factors and cytokines. Application of such markers may in time improve risk assessment and allow new treatment targets to be identified. Interventions that aim to achieve strict glycaemic control and blockade of the renin-angiotensin system have been shown to be effective in clinical trials and are feasible in clinical practice. The 'natural history' of diabetic nephropathy can be transformed these strategies of intensive screening and care applied, leading both to a lower incidence of diabetic nephropathy and to an improved outcome, with survival exceeding 20 years from onset of overt proteinuria.

24. Serum interleukin-18 levels are associated with nephropathy and atherosclerosis in Japanese patients with type 2 diabetes

Nakamura A, Shikata K, Hiramatsu M et al.

Diabetes Care 2005 28 (12): 2890-5.

Objective Interleukin (IL)-18 is a proinflammatory cytokine secreted from mononuclear cells. Serum concentration of IL-18 is a strong predictor of death in patients with cardiovascular diseases. Recent studies have shown that microinflammation is involved the pathogenesis of diabetic nephropathy as well as of cardiovascular diseases. This study aimed to test the hypothesis that the serum level of IL-18 is a common predictor of nephropathy and atherosclerosis in patients with type 2 diabetes. Research Design and Methods Eighty-two Japanese patients with type 2 diabetes and

55 age- and sex-matched healthy control subjects were enrolled. Patients with renal dysfunction (creatinine clearance < 1 ml/s) were excluded. We assessed clinical parameters and measured serum and urinary IL-18 levels, serum IL-6 levels, carotid intima-media thickness (IMT), and brachial-ankle pulse wave velocity (baPWV) in all patients. Further, we evaluated changes of urinary albumin excretion rate (AER) after 6 months in 76 diabetic patients. **Results** Serum and urinary IL-18 levels were significantly elevated in patients with type 2 diabetes as compared with control subjects (serum IL-18 179 +/- 62 vs. 121 +/- 55 pg/ml, $P < 0.001$; urinary IL-18 97 +/- 159 vs. 47 +/- 54 pg/ml, $P = 0.035$). Univariate linear regression analysis showed significant positive correlations between serum IL-18 and AER (r [correlation coefficient] = 0.525, $P < 0.001$). HbA(1c) ($r = 0.242$, $P = 0.029$), high-sensitivity C-reactive protein (hs-CRP) ($r = 0.240$, $P = 0.031$), and urinary beta-2 microglobulin ($r = 0.235$, $P = 0.036$). Serum IL-18 levels also correlated positively with carotid IMT ($r = 0.225$, $P = 0.042$) and baPWV ($r = 0.232$, $P = 0.040$). We also found a significant correlation between urinary IL-18 and AER ($r = 0.309$, $P = 0.005$). Multivariate linear regression analysis showed that AER (standard correlation coefficients [B] = 0.405, $P < 0.001$) and hs-CRP (B = 0.207, $P = 0.033$) were independently associated with serum IL-18 levels. AER was also independently associated with urinary IL-18 levels (B = 0.295, $P = 0.005$). Moreover, serum and urinary IL-18 levels correlated positively with AER after 6 months ($r = 0.489$, $P < 0.001$ and $r = 0.320$, $P = 0.005$) and changes in AER during the follow-up period ($r = 0.268$, $P = 0.018$ and $r = 0.234$, $P = 0.042$). **Conclusions** Serum levels of IL-18 might be a predictor of progression of diabetic nephropathy as well as cardiovascular diseases. _

25. An adult with acute poststreptococcal glomerulonephritis complicated by hemolytic uremic syndrome and nephrotic syndrome

Izumi T, Hyodo T, Kikuchi Y et al.

Am J Kidney Dis 2005 46 (4): e59-63.

We report the case of a 47-year-old man with the simultaneous occurrence of clinical and laboratory features consistent with acute poststreptococcal glomerulonephritis (APSGN), hemolytic uremic syndrome (HUS), and nephrotic syndrome. Acute nephritic syndrome occurred 3 weeks after having pharyngeal pain and diarrhea. He presented with edema and hypertension on admission. Laboratory evaluation showed hemolytic anemia with fragmentation, thrombocytopenia, elevated lactic dehydrogenase level, low haptoglobin level, low complement C3 level, and elevated antistreptolysin-O titer. Serum creatinine level was 1.22 (108 micromol/L), and urinalysis showed marked proteinuria, with protein of 8.7 g/d, and hematuria. The renal biopsy specimen was characteristic of APSGN, but not HUS. Moderate expansion of the mesangial matrix, moderate proliferation of epithelial and endothelial cells, and marked infiltration of neutrophils was seen by means of light microscopy, and many subepithelial humps seen by means of electron microscopy. Neither fibrin deposition nor evidence of thrombotic microangiopathy was found. Complement C3 deposition along capillary wall and tubules was seen in an immunofluorescence study. The patient was administered plasma infusion at 320 mL/d and antihypertensive drugs. Serum complement C3 and haptoglobin levels return to normal within 3 weeks. This is a rare case of the simultaneous occurrence of APSGN, HUS, and nephrotic syndrome.

26. Nephrotic range proteinuria and CD4 count as noninvasive indicators of HIV-associated nephropathy

Atta MG, Choi MJ, Longenecker JC et al.

Am J Med 2005 118 (11): 1288.

Purpose Human immunodeficiency virus (HIV)-associated nephropathy is a common and serious cause of progressive renal insufficiency in patients with HIV, frequently presenting with nephrotic range proteinuria. The purpose of this study is to document the histopathologic diagnosis seen in HIV-positive patients with and without nephrotic range proteinuria and to evaluate the predictive value of both nephrotic range proteinuria and CD4 count in diagnosing HIV-associated nephropathy.

Methods We performed a cross-sectional, single-center study of all 107 HIV-positive patients who had both a renal biopsy and urine protein measurement between 1995 and 2002. Nephrotic range proteinuria was defined as a urine protein-to-creatinine ratio > 3 or 24-hour urine protein > 3 g. Clinical and laboratory characteristics of those patients with and without HIV-associated nephropathy were compared. Sensitivity, specificity, and positive and negative predictive values of nephrotic range proteinuria in the diagnosis of HIV-associated nephropathy were determined.

Results Fifty-five biopsied patients had nephrotic range proteinuria, among whom 29 (53%) were diagnosed with HIV-associated nephropathy. Among the remaining patients, 12 had non-HIV-associated nephropathy focal segmental glomerulosclerosis, 3 had membranoproliferative glomerulonephritis, 2 had AA Amyloid, 2 had diabetic nephropathy, and 7 had other diagnoses. Sensitivity, specificity, and positive and negative predictive values of nephrotic proteinuria in the diagnosis of HIV-associated nephropathy were 73%, 61%, 53%, respectively. The patients with HIV-associated nephropathy had a significantly higher creatinine (8.2 mg/dL vs 2.5 mg/dL, $P < .001$) and a lower CD4 count (158 count/mm³ vs 349 count/mm³, $P < .01$) at the time of biopsy. Although significantly more patients with HIV-associated nephropathy had a CD4 count below 200 ($P = .03$), among those with a CD4 count below 200, 10 of 30 patients (33%) had diagnoses other than HIV-associated nephropathy. Injection drug use, presence of hepatitis C, and hypertension were not associated with HIV-associated nephropathy. **Conclusion** Our results suggest that HIV patients with nephrotic range proteinuria warrant a kidney biopsy because the presence of nephrotic range proteinuria, even in the presence of a low CD4 count, does not establish the diagnosis of HIV-associated nephropathy.

27. Autosomal recessive Alport syndrome: an in-depth clinical and molecular analysis of five families

Longo I, Scala E, Mari F et al.

Nephrol Dial Transplant 2005 Dec 7 [Epub ahead of print]

Background Alport syndrome (ATS) is a progressive inherited nephropathy characterized by irregular thinning, thickening and splitting of the glomerular basement membrane (GBM) often associated with hearing loss and ocular symptoms. ATS has been shown to be caused by COL4A5 mutations in its X-linked form and by COL4A3 and COL4A4 mutations in its autosomal forms.

Methods Five families with a suspicion of ATS were investigated both from a clinical and molecular point of view. COL4A3 and COL4A4 genes analysed by DHPLC. Automated sequencing was performed to identify the underlying mutation. **Results** Molecular analysis indicated that in all 5 cases the correct diagnosis was autosomal recessive ATS. In three families in which parental consanguinity clearly pinpointed to autosomal recessive ATS, we found COL4A4 homozygous mutations in two of them and COL4A3 homozygous mutation in the other one. In the remaining two families a differential diagnosis including X-linked ATS, autosomal recessive ATS and thin basement membrane nephropathy was considered. The molecular analysis demonstrated that the probands were genetic compounds for two different mutations in the COL4A4 gene pinpointing to the correct diagnosis of autosomal recessive ATS. **Conclusions** A clinical evaluation of probands and their relatives of the five families carrying mutations in either the COL4A3 or the COL4A4 gene was carried out to underline the natural history of the autosomal recessive ATS. In addition, this paper stresses complexity of the clinics and genetics of ATS and how a correct diagnosis is based on a combination of: (i) an in-depth clinical investigation; (ii) a detailed formal genetic analysis; (iii) a correct technical choice of the to be investigated; (iv) a correct technical choice of the family member to be included in the mutational screening. A correct diagnosis is the basis for an appropriate genetic risk for the patients and family members.

28. Identification of Fabry's disease by the screening of alpha-galactosidase A activity in male and female hemodialysis patients

Tanaka M, Ohashi T, Kobayashi M et al.

Clin Nephrol 2005 64 (4) 281-7.

Abstract Background Although previous studies reported that the prevalence of Fabry's disease was 0.16 – 1.2% in hemodialysis (HD) patients based on measurement of alpha-galactosidase A (alpha-Gal A) activity, few reports detected female patients by the screening for alpha-Gal A. Here we determined the prevalence of Fabry's disease not only in male but also in female HD patients by measuring alpha-Gal A. **Methods** Plasma alpha-Gal A was measured in 696 consecutive males (n = 401) and females (n = 295) on HD. Patients with low plasma alpha-Gal A were examined for leukocyte alpha-Gal A, and patients with low leukocyte alpha-Gal A underwent alpha-Gal A gene sequence analysis for possible mutations, and family survey. **Results** Among 15 patients with low plasma alpha-Gal A activity, 4 male patients with low leukocyte alpha-Gal A and 1 female patient revealing low plasma alpha-Gal A were detected in 696 HD patients (0.7% of total patients). 3 of these 5 patients were already diagnosed to have classical type of Fabry's disease. The other 2 patients were newly diagnosed as Fabry's disease, and did not have typical manifestations of Fabry's disease other than renal failure and left ventricular hypertrophy. DNA analysis of these 2 newly diagnosed patients revealed that each had an alpha-Gal missense mutation, previously identified (E66Q, M296I). **Conclusion** Fabry's disease should be considered in the etiology of unexplained end-stage renal disease. Not only affected males but also affected females undergoing HD patients can be readily diagnosed by alpha-Gal A activities and gene analysis. These patients and their family members may benefit from enzyme replacement therapy for Fabry's disease.

V. TREATMENT

1. Low-dose dual blockade of the renin-angiotensin system improves tubular status in non-diabetic proteinuric patients

Renke M, Tylicki L, Rutkowski P et al.

Scand J Urol Nephrol 2005 39 (6): 511-7.

Objective Treatment with agents that inhibit the renin-angiotensin system is commonly regarded as a gold standard renoprotective strategy in patients with chronic kidney diseases. For maximum antiproteinuric effect, the dose titration of these agents is recommended. This therapeutic strategy is not used for proteinuric patients who are not able to receive high doses of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonists. **Material and Methods** In patients with primary glomerulonephritis (n=24), a randomized, triple-treatment, triple-period, cross-over study was performed to compare the effects of combined therapy with benazepril 5 mg and losartan 25 mg and monotherapy with either agent alone at a two-fold higher dose on the extent the plasma level of transforming growth factor-beta1 (TGF-beta1). **Results** Combination therapy significantly reduced alpha1-m excretion compared to either agent used alone: 178.29 +/- 27.36 to 99.63 +/- 13.03 mg/g creatinine losartan + benazepril vs 178.29 +/- 27.36 to 161.59 +/- 23.22 mg/g creatinine for benazepril alone (p<0.05; ANOVA) and 178.29 +/- 27.36 to 99.63 +/- 13.03 mg/g creatinine for losartan + benazepril vs 178.29 +/- 173.45 +/- 27.69 mg/g creatinine for losartan alone (p<0.05; ANOVA). There was a significant correlation between change in alpha1-m excretion and reduction in proteinuria (r=0.704; P=0.023). There were no differences in TGF-beta1 level between the studied treatments. Systemic blood pressure reduction did not differ among the therapies.

Conclusions Combination therapy with angiotensin-converting enzyme inhibitor and angiotensin II subtype 1 receptor antagonists at very small doses may be superior to monotherapy with these agents at higher doses as far as tubular injury concerned. We speculate that such a therapeutic strategy may be a useful approach for patients who are known not to be capable of receiving optimal renoprotective doses of these regimens.

2. Effect of low-dose dual blockade of renin-angiotensin system on urinary TGF- β in type 2 diabetic patients with advanced kidney disease

Ho Song J, Ho Cha S, Jae Lee H et al.

Nephrol Dial Transplant 2005 Dec 5 [Epub ahead of print]

Background We evaluated the renoprotective effects of dual blockade of renin-angiotensin system (RAS) by using a low-dose combination of ACE inhibitor and angiotensin II receptor blocker in type 2 diabetic patients with advanced kidney disease. The amount of proteinuria and the urinary levels of bioassayable TGF-beta1 were used as surrogate markers of renal injury and sclerosis.

Methods We performed a prospective double-blinded randomized crossover trial consisting of three 16-week treatment periods with ramipril alone (10 mg/day), candesartan alone (16 mg/day), and ramipril 5 mg/day plus candesartan (8 mg/day) combination therapy. Twenty-one type 2 diabetic patients with overt nephropathy with a 24h urinary protein excretion rate (UPER) of >1.0 g/24h and creatinine clearance (Ccr) of 30 to 59 ml/min/1.73m(2) completed the entire study.

Results Subjects consisted of 10 female and 11 male patients with mean age of 49 +/- 8 years and duration of diabetes ranging from 4 to 13 years. At baseline, 24-h blood pressures (BPs) were 133 +/- 6/81 +/- 7 mmHg, Ccr 40.6 +/- 4.1 ml/min/1.73m(2), 24-h UPER 4.1 +/- 1.9 g/24h, and urinary TGF-beta1 level 28.4 +/- 16.1 pg/mg creatinine (cr). Although there was no comparable change in BP and plasma/urinary biochemical parameters, 24-h UPER was significantly reduced by combination therapy (2.9 +/- 1.4 g/24h) compared with that of ramipril (3.5 +/- 1.8 g/24h) and of candesartan (3.3 +/- 2.0 g/24h) single therapy (P <0.05). urinary TGF-beta1 level was reduced in all three therapies compared with that of the control (28.4 +/- 16.1 pg/mg cr) (P<0.05). However, the combination therapy showed the most significant change (combination 19.6 +/- 10.6 pg/mg cr; ramipril 24.7 +/- 13.3 pg/mg cr; candesartan 23.4 +/- 11.7 pg/mg cr). No significant or irreversible adverse effect was observed in the 21 patients who completed the entire study. **Conclusions** The dual blockade of RAS with low-dose ramipril plus candesartan was found to be safe and offered additive benefits with respect to reducing proteinuria and urinary TGF-beta1 excretion in diabetic patients with advanced kidney disease. These benefits were evident as compared with single ramipril and candesartan therapies at doses two-fold greater. Further study on the dose-titration is mandatory in terms of safety and especially for maximizing renoprotection in this patient population. _

3. Renal protective effects of the renin-angiotensin-aldosterone system blockade: from evidence-based approach to perspectives

Tylicki L, Larczynski W, Ruktowski B.

Kidney Blood Press Res 2005 28 (4): 230-242

The renin-angiotensin-aldosterone system (RAAS) blockade is currently the best-documented treatment strategy to delay the progression of chronic nephropathies. Angiotensin-converting enzyme inhibitors (CEIs) or angiotensin II type 1 receptor antagonists (ARBs) should be used in every normotensive and hypertensive patient with chronic proteinuric nephropathy of diabetic and non-diabetic origin. The therapy should be initiated as early as possible, bearing in mind that the renoprotection is more effective if used before overt proteinuria or a reduction in kidney function is present. The therapy should be offered to all patients, regardless of renal function, as well as to subjects with severely impaired glomerular filtration. CEIs and ARBs should be administered in therapeutic doses as high as possible to achieve maximal possible proteinuria reduction and systemic blood pressure target <130/80 mm Hg, and 125/75 mm Hg in those subjects with renal insufficiency who present with proteinuria above 1 g/24 h. The combined therapy with the concomitant use of CEIs and ARBs should be offered to all patients with proteinuric non-diabetic chronic nephropathies who do not achieve full and persistent remission of proteinuria with CEI or ARB alone.

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

Butani L.

Pediatr Nephrol 2005 20 (11): 1651-4.

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

5. Prevention of progression and remission/regression strategies for chronic renal diseases: can we do better now than five years ago?

Perico N, Codreanu I, Schieppati A et al.

Kidney Int Suppl 2005 (98): S21-4.

The prevalence of chronic renal diseases is increasing worldwide. There is a great need to identify therapies that arrest disease progression to end-stage renal failure. Inhibition of renin-angiotensin system both by ACE inhibitors and angiotensin II receptor antagonists is probably the best therapeutic option available. Several large, multicenter studies have indeed shown a significant reduction in risk of doubling baseline serum creatinine or progression toward end-stage renal failure in diabetic and nondiabetic patients with chronic nephropathies treated with ACE inhibitors or angiotensin II receptor antagonists. However, the number of patients that reach end-stage renal failure is still considerably high. Significant reduction of the incidence of end-stage renal disease is likely to be achieved in the next future for chronic nephropathies, provided that we can improve the degree of renoprotection. This goal may be attainable with a more complex strategy than with a single or dual pharmacologic intervention on the renin-angiotensin system. Strict control of blood pressure and protein excretion rate, lowering of blood lipids, tight glucose control for diabetics, and lifestyle changes form part of the future multimodel protocol for management of patients with chronic nephropathies.

6. Antihypertensive agents for primary prevention of diabetic nephropathy

Strippoli GF, Craig M, Schena FP et al.

J Am Soc Nephrol 2005 16 (10): 3081-91.

The objective of this study was to evaluate the comparative effects of antihypertensive agents in patients with diabetes and normoalbuminuria. Randomized, controlled trials that compared any antihypertensive agent with placebo or another agent in hypertensive or normotensive patients with diabetes and normoalbuminuria (albumin excretion rate <30 mg/d) were identified on Medline, in Embase, on the Cochrane Controlled Trials Register, in conference proceedings, and by contacting investigators. Two authors independently extracted data on renal outcomes and other patients-relevant outcomes (e.g., mortality, serious cardiovascular events) and assessed quality of trials. Analysis was by a random-effects model, and results were expressed as relative risk (RR) and 95% confidence intervals (CI). Sixteen trials (7603 patients) were identified, six of angiotensin-converting enzyme inhibitors (ACEi) versus placebo, six of ACEi versus calcium antagonists, one of ACEi versus calcium antagonists or combined ACEi and calcium antagonists, and three of ACEi versus other agents. Compared with placebo, ACEi significantly reduced the development of microalbuminuria (six trials, 3840 patients; RR 0.60; 95% CI 0.43 to 0.84) but not doubling of creatinine (three trials, 2683 patients; RR 0.81; 95% CI 0.24 to 2.71) or all-cause mortality (four trials, 3284 patients; RR 0.81; 95% CI 0.64 to 1.03). Compared with calcium antagonists, ACEi significantly reduced progression to microalbuminuria (four trials, 1210 patients; RR 0.58; 95% CI 0.40 to 0.84). A significant reduction in the risk for developing microalbuminuria in normoalbuminuric patients with diabetes has been demonstrated for ACEi only. It seems that the effect of ACEi is independent of baseline BP, renal function, and type of diabetes, but data are too sparse to be confident that these are not important effect modifiers, and an individual patient data meta-analysis is required.

7. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria

Rossing K, Schjoedt KJ, Jensen BR et al.

Kidney Int 2005 68 (3): 1190-8.

Background The purpose of this study was to evaluate the renoprotective effect as reflected by short-term changes in albuminuria of ultrahigh doses of irbesartan in type 2 diabetic patients with microalbuminuria. **Methods** This double-masked randomized crossover trial included 52 (41 males) hypertensive type 2 diabetic patients with microalbuminuria on ongoing antihypertensive medication. At inclusion, previous antihypertensive treatment was discontinued and replaced with bendroflumethiazide, 5 mg once daily, for the entire study. Following 2 months wash-out (baseline), patients were treated randomly with irbesartan 300, 600, and 900 mg once daily, each dose for 2 months. End points evaluated at the end of each study period included urinary albumin excretion rate (UAE) (mean of three 24-hour collections), 24-hour ambulatory blood pressure, and glomerular

filtration rate (GFR) [chromium 51 ethylenediaminetetraacetic acid (51)Cr-EDTA)]. Results baseline values were: 24-hour UAE [geometric mean (95% CI)] 134 (103 to 170) mg/24 hours, ambulatory blood pressure [mean (SD)] 140 (10) / 77 (7) mm Hg, and GFR 103 (19) mL/min/1.73 m². All doses of irbesartan significantly reduced UAE, ambulatory blood pressure, and GFR from baseline. Reduction in UAE from baseline were 52% (46% to 57%), 49% (43% to 54%), and 59% (54% to 63%) with increasing doses of irbesartan ($P < 0.01$). UAE was reduced significantly more by irbesartan 900 mg compared with lower doses with an additional reduction in UAE of 15% (2% to 26%) by irbesartan 900 mg compared with 300 mg ($P = 0.02$). The greater reduction in albuminuria by irbesartan 900 vs. 300 mg was more pronounced in patients with UAE during irbesartan 300 mg above vs. below the median [31% (18% to 42%) vs. -9% (-25% to 6%), respectively ($P < 0.05$)]. With increasing doses systolic ambulatory blood pressure was reduced from baseline by 8 (4 to 12), 9 (5 to 13) mm Hg, and diastolic ambulatory blood pressure by 6 (4 to 7), 7 (6 to 9) and 7 (6 to 9) mmHg (NS between doses). Conclusion Ultrahigh dosing of irbesartan (900 mg once daily) is generally safe and offers additional renoprotection independent of changes in systemic blood pressure and GFR in comparison to the currently recommended dose of 300 mg.

8. An update of irbesartan and renin-angiotensin system blockade in diabetic nephropathy

Garcia-Donaire JA, Segura J, Ruilope LM.

Expert Opin Pharmacother 2005 6 (9): 1587-96.

Type 2 diabetes is a chief cause of pathologies such as cardiovascular disease, nephropathy and retinopathy, and its prevalence is increasing worldwide. Development of renal disease can be slowed by tight glycaemic control and treatment of associated hypertension with angiotensin-converting enzyme inhibition, as The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study have demonstrated. Recent clinical trials have supported the use of angiotensin II receptor antagonists in the treatment of diabetic nephropathy, resulting in the approval of new therapeutic indications in the US and Europe. The main goal of this review is to demonstrate how results from Programme for Irbesartan Mortality and Morbidity Evaluation and other recent studies, based on the effects of renin-angiotensin system blockade, can be appropriate in clinical practice, thus displaying benefits of irbesartan therapy at any stage of renal disease in diabetics.

9. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial: clinical implications and limitations

Pohl MA, Blumenthal S, Cordonnier DJ et al.

J Am Soc Nephrol 2005 16 (10): 3027-37.

Elevated arterial pressure is a major risk factor for progression to ESRD in diabetic nephropathy.

However, the component of arterial pressure (BP) and level of BP control for optimal renal outcomes are disputed. Data from 1590 hypertensive patients with type 2 diabetes in the Irbesartan Diabetic Nephropathy Trial (DDNT), a randomized, double-blind, placebo-controlled trial performed in 209 clinics worldwide, were examined, and the effects of baseline and mean follow-up systolic BP (SBP) and diastolic BP and the interaction of assigned study medications (irbesartan, amlodipine, and placebo) on progressive renal failure and all-cause mortality were assessed. Other antihypertensive agents were added to achieve predetermined BP goals. Entry criteria included elevated baseline serum creatinine concentration up to 266 $\mu\text{mol/L}$ (3.0 mg/dl) and urine protein excretion >900 mg/d. Baseline BP averaged 159/87 \pm 20/11 mmHg. Median patient follow-up was 2.6 yr. Follow-up achieved SBP most strongly predicted renal outcomes. SBP >149 mmHg was associated with a 2.2-fold increase in the risk for doubling serum creatinine or ESRD compared with SBP <134 mmHg. Progressive lowering of SBP to 120 mmHg was associated with improved renal and patient survival, an effect independent of baseline renal function. Below this threshold, all-cause mortality increased. An additional renoprotective effect of irbesartan, independent of achieved SBP, was observed down to 120 mmHg. There was no correlation between diastolic BP and renal outcomes. We recommend a SBP target between 120 and 130 mmHg, in conjunction with blockade of the renin-angiotensin system, in patients with type 2 diabetic nephropathy.

10. Irbesartan reduces creatinine clearance in type 1 diabetic children with renal hyperfunction: double-blind, placebo-controlled trial

Salcedo-Alejos M, Banda-Espinoza F, Rodriguez-Morán M et al.

Nephrol Dial Transplant 2005 (20): 2120-5.

Abstract **Background** Previous studies in type 2 diabetes have demonstrated the renoprotective effects of AT1-receptor antagonist drugs, but data on type 1 diabetic (T1DM) children are scarce. The aim of this study was to evaluate the effectiveness of the AT1-receptor antagonists irbesartan in reducing creatinine clearance rate (CCR) in non-hypertensive T1DM children with renal hyperfunction. **Methods** In this randomized, double-blind, placebo-controlled trial we enrolled 20 T1DM children aged 6-16 years and randomly allocated them to receive either irbesartan (1mg/kg body weight) or placebo daily for 12 weeks. Children were eligible to participate if they had renal hyperfunction, defined as a CCR $>20\text{ml/min/1.73m}^2$ body surface area. In addition, the participants could not have high blood pressure or renal failure and they could not be receiving diuretics or angiotensin-converting enzyme inhibitors. The primary endpoint of the trial was the change in CCR. **Results** There were no significant differences in age, duration of diabetes or body mass index between the two groups. No subject dropped out, withdrew consent or had side effects or adverse events attributable to irbesartan or the placebo. In the irbesartan group, CCR decreased from 155.0 ± 6.6 to 86.2 ± 7.4 ml/min (P <0.0001); did not change significantly in the control group (154 ± 13.1 to 172.0 ± 15.5 ml/min; PP=0.86). Blood pressure at baseline and throughout the study were similar in both groups. **Conclusion** Irbesartan significantly reduces CCR in non-hypertensive, non-controlled T1DM children; the clinical significance of this finding, however, remains to be established.

11. Candesartan reduces urinary fatty acid-binding protein excretion in patients with autosomal

dominant polycystic kidney disease

Nakamura T, Sugaya T, Kawagoe Y et al.

Am J Med Sci 2005 330 (4): 161-5.

Background Free fatty acids (FFAs) bound to albumin are overloaded in renal proximal tubules and exacerbate tubulointerstitial damage. Live-type fatty acid-binding protein (L-FABP) is an intracellular carrier protein of FFAs that is expressed in renal proximal tubules in human. Urinary L-FABP reflects the clinical prognosis of chronic glomerulonephritis. The aim of the present study was to determine whether urinary L-FABP excretion is altered in patients with autosomal dominant polycystic kidney disease (ADPKD) and whether candesartan cilexetil, an angiotensin II receptor antagonists, affects these levels. **Methods** Subjects comprised 20 normotensive ADPKD patients (8 men and 12 women, mean age 42.6 years) and 20 age-matched healthy volunteers (8 men 12 women, mean age 44.0 years). The 20 ADPKD patients participated in a randomized double-blind placebo-controlled study of candesartan cilexetil for 6 months. Urinary L-FABP levels were measured by a newly established ELISA method. **Results** Urinary L-FABP levels were significantly higher in ADPKD patients (145.5 +/- 110.6 mug/g Cr) than in healthy subjects (5.5 +/- 3.8 mug/g Cr) ($P < 0.001$). candesartan cilexetil reduced urinary L-FABP levels from 168.5 +/- 104.5 mug/g Cr to 98.5 mug/g Cr after 3 months ($P < 0.01$) and to 44.6 +/- 30.8 mug/g Cr after 6 months ($P < 0.001$). Placebo had no effect on L-FABP levels (before, 140.5 +/- 100.5 mug/g Cr; at 3 months, 148.5 +/- 108.5 mug/g Cr; at 6 months, 150.5 +/- 110.8 mug/g Cr). During the 6 months, serum creatinine, blood urea nitrogen, 24-hour creatinine clearance and blood pressure showed little change in either group. **Conclusion** Increased urinary L-FABP may be associated with the development of ADPKD, and candesartan cilexetil has a beneficial effects on reducing these levels.

12. Effects of losartan and amlodipine on urinary albumin excretion and ambulatory blood pressure in hypertensive type 2 diabetic patients with overt nephropathy

Yasuda G, Ando D, Hirawa N et al.

Diabetes Care 2005 28 (8): 1862-8.

Objective Few studies have assessed whether 24-h blood pressure control induced by antihypertensive agents improves macroalbuminuria in hypertensive type 2 diabetic patients with overt nephropathy. We evaluated the effects of losartan and amlodipine on 24-h blood pressure, autonomic nervous activity, and albuminuria in these patients. **Research Design and Methods** In this open-label, parallel-prospective, randomized study, 44 patients were treated with losartan and 43 with amlodipine for a 12-week titration phase and a maintenance phase for a maximum of 12 weeks. Twenty-four-hour blood pressure and urinary albumin excretion were measured before and during treatment. Simultaneously, power spectral analysis of heart rate was performed to evaluate low frequency (LF) and high frequency (HF) components and LF-to-HF- ratios as an index of sympathovagal balance. **Results** Losartan decreased ($p < 0.001$) mean blood pressure from 162/91 to 150/82 mmHg during daytime and from 146/82 to 137/74 mmHg during nighttime (systolic/diastolic). Amlodipine also decreased ($P < 0.001$) blood pressure from 159/90 to 147/82

mmHg during daytime and from 143/81 to 131/72 mmHg during nighttime. LF and HF components and nighttime-to-daytime ratios for the LF-to-HF ratios did not differ during treatment in two groups, showing no change in the diurnal autonomic nervous rhythm. Losartan decreased ($P < 0.001$) 24-h urinary albumin excretion from 810 mg/day (95% CI 780-1, 140) to 570 (510-910). Amlodipine, however, did not decrease ($P = 0.893$) albuminuria (790 mg/day [780-1, 170] vs. 790 [710-1, 260]). Conclusion These suggest that in type 2 diabetes with overt nephropathy, 24-h blood pressure regulation alone is inadequate to reduce macroalbuminuria and addition effects of losartan are crucial for antiproteinuric action.

13. Calcium antagonists: effects of cardio-renal risk in hypertensive patients

Nathan S, Pepine CJ, Bakris GL.

Hypertension 2005 46 (4): 637-42.

Calcium antagonists comprise 2 main subclasses, dihydropyridines and nondihydropyridines, and have been studied extensively in hypertensive patients. Early meta-analyses suggested that short-acting calcium antagonists were associated with higher mortality rates resulting from cardiovascular events and other etiologies. Recent meta-analysis failed to show any substantive difference between long acting calcium antagonists and other antihypertensive drug classes with regard to cardiovascular outcomes in those with low to moderate cardiovascular risk or kidney disease progression among those with stage 2 or 3 nonproteinuric kidney diseases. The data from calcium antagonist trials are consistent in that they decrease stroke incidence but fail to protect against new-onset heart failure. In people with proteinuric kidney disease, that is > 300 mg protein/gram creatinine, use of dihydropyridine calcium antagonists to lower blood pressure without the use of agents that block the renin angiotensin aldosterone system does not provide optimal slowing of nephropathy progression. This relates directly to lack of antiproteinuric effects with this subclass and not seen with nondihydropyridine agents that reduce proteinuria to a greater degree than dihydropyridines. Thus, calcium antagonists are safe and as efficacious as other antihypertensive agents to reduce cardiovascular risk. They should be avoided in people with systolic dysfunction but may be used for blood pressure lowering in people with preserved systolic function. Dihydropyridine calcium antagonists should be used in conjunction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in proteinuric kidney disease because they will not optimally slow kidney function loss in their absence.

14. The role of calcium antagonists in patients with chronic renal failure

Rahn KH.

Pediatr Nephrol 2005 20 (9): 1208-13.

The objective of antihypertensive treatment in patients with chronic renal failure, many of whom have elevated blood pressure levels, is to reduce cardiovascular events and to slow the progression

of kidney function impairment. Calcium antagonists have been shown to be effective and safe antihypertensive drugs in patients from different age groups, including children. On the basis of numerous studies, one may conclude that the main benefit of antihypertensive therapy is because of the blood pressure lowering effect per se and that calcium antagonists do not differ from other antihypertensive drugs in the ability to prevent cardiovascular complications of hypertension. In particular, calcium antagonists are not inferior to other groups of antihypertensive agents in the prevention of coronary artery disease. There is, however, now evidence from controlled trials that drugs interfering with the renin-angiotensin system are more beneficial than other antihypertensive agents in patients with chronic renal failure. Thus, several studies have demonstrated that ACE-inhibitors and, in patients with type 2 diabetic nephropathy. AT 1-antagonists are superior to other classes of antihypertensive drugs, including calcium antagonists, in delaying the progression of renal insufficiency. Therefore, in hypertensive patients with chronic renal failure antihypertensive treatment should be initiated with a drug that inhibits the renin-angiotensin system.

15. Beneficial impact of spironolactone in diabetic nephropathy

Schjoedt KJ, Rossing K, Juhl TR et al.

Kidney Int 2005 68 (6): 2829-36.

Background Aldosterone has been suggested to play a role in the initiation and progression of diabetic nephropathy. Currently recommended treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers [renin-angiotensin system (RAS) blockade] does not suppress circulating aldosterone sufficiently. We therefore aimed to evaluate the short-term effect of aldosterone antagonism with spironolactone on albuminuria and blood pressure in diabetic nephropathy. **Methods** Twenty Caucasian type 1 diabetic patients with persistent macroalbuminuria despite antihypertensive treatment, including RAS blockade, completed this double-masked, randomized cross-over trial. Patients were treated in random order with spironolactone 25mg once daily and matched placebo for two months, respectively, on top of usual antihypertensive treatment. After each treatment period albuminuria, 24-hour blood pressure, and glomerular filtration rate (GFR) were determined. **Results** Spironolactone on top of usual antihypertensive treatment induced a 30% (95% CI 17 to 41) reduction in albuminuria from [geometric mean (95% CI)] 831 (624 to 1106) mg/24-hour on placebo treatment ($P < 0.001$), and a reduction in fractional albumin clearance of 35% (20 to 46, $P < 0.001$). Twenty-four-hour blood pressure showed an insignificant reduction of [mean reduction (95% CI) 8 (-1 to 17)/3 (-0.2 to 7) mm Hg ($P < 0.10$). There was an insignificant reversible reduction in GFR during treatment with spironolactone. On spironolactone treatment, one patient was excluded due to hyperkalemia (plasma potassium 5.7 mmol/L) and one due to orthostatic dizziness. Otherwise treatment was well tolerated. **Conclusion** Our results suggest that spironolactone treatment on top of recommended antihypertensive treatment reduces blood pressure and may offer additional renoprotection in type 1 diabetic patients with diabetic nephropathy.

16. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study

Rossing K, Schjoedt KJ, Smidt UM et al.

Diabetes Care 2005 28 (9): 2106-12.

Objective The objective of this study was to evaluate the safety and short-term effect of adding spironolactone to conventional antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor or an angiotensin II receptor blocker (ARB) on albuminuria and blood pressure in type 2 diabetic patients with nephropathy. **Research Design and Methods** Twenty-one type 2 diabetic patients with nephropathy were enrolled in a randomized, double-masked cross-over study. Patients were treated in random order with spironolactone 25 mg once daily and matched placebo for 8 weeks, respectively, in addition to ongoing antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor and/or ARB. At the end of each treatment period, albuminuria, 24-h ambulatory blood pressure (ABP), and glomerular filtration rate (GFR) were determined. **Results** During the addition of placebo, values were as follows: albuminuria (geometric mean [range] 1.566 [655-7, 762] mg/24 h, ABP (mean \pm SE) 138 \pm 3/71 \pm 1 mmHg, and GFR (mean \pm SE) 74 \pm 6 ml/min per 1.73 m². During the addition of spironolactone, albuminuria was reduced by 33% (95% CI 25-41) ($P < 0.001$), fractional clearance of albumin by 40% (24-53) ($P < 0.001$) and 24-h ABP by 6 mmHg (2-10) for systolic and 4 mmHg (2-6) for diastolic ($P < 0.001$ for both). The change in albuminuria did not correlated with change in systolic 24-h ABP ($r = 0.19$, $P = 0.42$) or diastolic 24-h ABP ($r = 0.01$, $P = 0.96$). Spironolactone treatment induced an insignificant reversible reduction in GFR of 3 ml/min per 1.73 m² (-0.3 to 6) ($P = 0.08$). One patient was excluded from the study due to hyperkalemia. Otherwise treatment was well tolerated. **Conclusion** Our study suggest that spironolactone safely adds to the reno- and cardiovascular protective benefits of treatment with maximally recommended doses of ACE inhibitor and ARB by reducing albuminuria and blood pressure in type 2 diabetic patients with nephropathy.

17. The role of statins in chronic kidney disease

Agarwal R, Curley TM.

Am J Med Sci 2005 330 (2): 69-81.

Chronic kidney disease is associated with cardiovascular event rates that are at least as high as in patients with established atherosclerotic cardiovascular disease or in those with diabetes mellitus. Chronic kidney disease is therefore considered a cardiovascular disease risk equivalent. Treatment of dyslipidemia which is very common in this population and reflects the pattern seen in the metabolic syndrome, reduces cardiovascular events in patients with chronic kidney disease. Thus, patients with chronic kidney disease should be evaluated and treated for dyslipidemia. Dyslipidemia is a risk factor for the development of impaired kidney function. Dyslipidemia is also associated with progressive renal disease in subjects with no overt renal disease, as well as those with diabetic and nondiabetic kidney disease. Although definitive randomized controlled trial are lacking, the collective evidence suggest that treatment of dyslipidemia is associated with less decline in renal function. The use of potent statins in high doses can lead to transient proteinuria via impairment of proximal tubular receptor – mediated endocytosis, in a dose-dependent manner. Over the long term, however, the use of statins results in a reduction in proteinuria and in the rate of decline of renal

function. Several large definitive trials that are currently underway to examine the safety and efficacy of statins in cardiovascular and renal protection should provide more definitive answers on the role of these drugs in this very high risk population.

18. Statins in nephrotic syndrome: A new weapon against tissue injury

Buemi M, Nostro L, Crasci E et al.

Med Res Rev 2005 25 (6): 587-609.

The nephrotic syndrome is characterized by metabolic disorders leading to an increase in circulating lipoproteins levels. Hypertriglyceridemia and hypercholesterinemia in this case may depend on a reduction in triglyceride-rich lipoproteins catabolism and on an increase in hepatic synthesis of Apo B-containing lipoproteins. These alterations are the starting point of a self-maintaining mechanism, which can accelerate the progression of chronic renal failure. Indeed, hyperlipidemia can affect renal function, increase proteinuria and speed glomerulosclerosis, thus determining a higher risk of progression to dialysis. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme in cholesterol synthesis from mevalonate and its inhibitors, or statin, can therefore interfere with the above-mentioned consequences of hyperlipidemia. Statins are already well known for their effectiveness on primary cardiovascular prevention, which cannot be explained only through their hypolipemic effect. As far as kidney diseases are concerned, statin therapy has been shown to prevent clearance decline and to slow renal function loss, particularly in case of proteinuria, and its favorable effect depend only partially on the attenuation of hyperlipidemia. Statins may therefore confer tissue protection through lipid-independent mechanisms, which can be triggered by other mediators, such as angiotensin receptor blockers. Possible pathways for the protective action statins, other than any hypocholesterolemic effect, are: cellular apoptosis/proliferation balance, inflammatory cytokines production, and signal transduction regulation. Statins also play a role in the regulation of the inflammatory and immune response, coagulation process, bone turnover, neovascularization, vascular tone, and arterial pressure. In this study, we would like to provide scientific evidences for the pleiotropic effects of statins, which could be the starting point for the development of new therapeutical strategies in different clinical areas.

19. Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy

Nakamura T, Sugaya T, Kawagoe Y et al.

Diabetes Care 2005 28 (11): 2728-32.

Objective Liver-type fatty acid-binding protein (1-FABP) is expressed in renal proximal tubules and is reported to be useful marker for progression of chronic glomerulonephritis. The aim of this study was to determine whether urinary 1-FABP levels are altered at various stages of diabetic

nephropathy and whether pitavastatin affects urinary 1-FABP levels in early diabetic nephropathy. **Research Design and Methods** Fifty-eight patients with type 2 diabetes (34 men and 24 women, median age 52 years) and 20 healthy, age-matched subjects (group E) were recruited for the study. The diabetic patients included 12 patients without nephropathy (group A), 20 patients with microalbuminuria (group B), 14 patients with macroalbuminuria and normal renal function (group C), and 12 patients with chronic renal failure but not undergoing hemodialysis (blood creatinine >1.2 mg/dl; mean 2.5 mg/dl, group D). Twenty group B patients were randomly assigned to receive 1 mg/day pitavastatin (10 patients, group B1) or placebo (10 patients, group B2). Treatment was continued for 12 months. Urinary 1-FABP levels measured by enzyme-like immunosorbent assay. Urinary 8-hydroxydeoxyguanosine and serum free fatty acids (FFAs) were also measured in group B. **Results** Urinary 1-FABP levels in groups A-D were 6.2 +/- 4.6 microg/g creatinine, 19.6 +/- 13.5 microg/g creatinine, 26.8 +/- 20.4 microg/g creatinine, and 52.4 +/- 46.8 microg/g creatinine, respectively. Urinary 1-FABP levels in groups B-D were significantly higher than those in healthy subjects (group E, 5.8 +/- 4.0 microg/g creatinine) (group B, $P < 0.05$; group C, $P < 0.01$; group D, $P < 0.01$). In group B1, urinary albumin excretion (UAE) and urinary 1-FABP levels were decreased after pitavastatin treatment (UAE before, 110 +/- 74 microg/min; 6 months, 88 +/- 60 microg/min, $P < 0.05$; 12 months, 58 +/- 32 microg/min, $P < 0.01$; 1-FABP before, 18.6 +/- 12.5 microg/g creatinine; 6 months 12.2 +/- 8.8 microg/g creatinine, $P < 0.05$; 12 months, 8.8 +/- 6.4 microg/g creatinine, $P < 0.01$). In group B2, UAE and 1-FABP levels showed little change during the experimental period. In group B1, urinary 8-hydroxydeoxyguanosine was decreased 12 months after pitavastatin treatment (before 32.5 +/- 19.5 ng/mg creatinine, after 18.8 +/- 14.5 ng/mg creatinine, $P < 0.01$). but in group B2, these showed little difference during experimental period. In both groups B1 and B2, serum FFAs showed little difference during the experimental period. **Conclusion** Urinary 1FABP levels appear to be associated with the progression of diabetic nephropathy, and pitavastatin may be effective in ameliorating tubulointerstitial damage in early diabetic nephropathy.

20. N-3 fatty acid supplementation decrease plasma homocysteine in diabetic dyslipidemia treated with statin-fibrate combination.

Zeman M, Zak A, Vecka M et al.

J Nutr Biochem 2005 Oct 5 [Epub ahead of print]

The aim of this study was to study the effect of adding polyunsaturated fatty acid (PUFA) n-3 or placebo (containing oleic acid) to a combined statin-fibrate treatment on plasma lipoproteins, lipoperoxidation, glucose homeostasis, total homocysteine (tHcy) and microalbuminuria (MA) in patients with diabetic dyslipidemia (DDL). Twenty-four patients, who did not fulfill the recommended target lipid values with combined hypolipidemic therapy (pravastatin 20 mg + micronized fenofibrate 200 mg daily), were supplemented with 3.6 g PUFA n-3 daily for 3 months or placebo (olive oil) for the next 3 months. The concentrations of plasma lipids, fatty acid (FA) profiles or phosphatidylcholine (PC), cholesteryl esters (CE) and triglycerides (TG), tHcy levels, concentration of conjugated dienes (CD) in low-density lipoprotein (LDL), and MA were determined in baseline state, after the PUFA n-3 and placebo treatment period. Supplementation with PUFA n-3 led to a significant decrease in plasma tHcy (-29%, $P < .01$) and TG (-28%, $P < .05$) levels, as well as to a significant decrease in MA (-24%, $P < .05$). The decrease in MA correlated significantly with the increase in total PUFA n-3 ($r = -.509$, $P < .05$) and docosahexaenoic acid ($r = -.52$, $P < .01$) in TG. The concentrations of CD in LDL increased significantly (+15%, $P < .05$). The supplementation with PUFA n-3 to the combined statin-fibrate treatment in patients with DDL

decreased the TG and tHcy levels as well as MA. It could lead to decreased risk of atherothrombosis and delay of diabetic nephropathy onset and progression.

21. Statin therapy reduces contrast-induced nephropathy: An analysis of contemporary percutaneous interventions.

Khanal S, Attalah N, Smith DE et al.

Am J Med 2005 118 (8): 843-9.

Abstract Purpose We sought to examine statin therapy before percutaneous coronary intervention results in reduction in contrast-induced nephropathy (CIN). Intravascular administration of contrast media can have nephrotoxic effects, particularly in patients with baseline renal insufficiency. Along with lowering serum cholesterol, statins have pleiotropic effects in the vasculature. The effect of statin use on CIN is unknown. Subjects and Methods We studied 29 409 patients who had both baseline preprocedure and peak postprocedure serum creatinine measured at the time of their percutaneous coronary intervention (PCI). Baseline demographics and creatinine profile before and after the procedure were compared between patients who received preprocedure statins and those who did not. CIN was defined as an increase in serum creatinine of ≤ 0.5 mg/dL. Results Baseline serum creatinine was similar between the two groups. When compared with patients who did not receive statins, patients on preprocedure statins had a lower incidence of CIN (4.37 vs 5.93, $P < 0.0001$) and nephropathy requiring dialysis (0.32 vs 0.46, $P = 0.03$). After adjustments for comorbidities, preprocedure statin use was associated with a significant reduction in CIN (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.77-0.99, $P = 0.03$). Conclusions Preprocedure statin use is associated with significant reduction in CIN after contemporary PCI. This reinforces the need to initiate statin before percutaneous coronary interventions.

22. PPAR-gamma-agonists' renal effects

Izzedine H, Launay-Vacher V, Buhaescu I et al.

Minerva Urol Nefrol 2005 57 (4): 247-60.

PPAR-gamma ligands, including thiazolidinediones, have recently become clinically available for treating insulin-resistant diabetes mellitus. Accumulating evidence suggests that drugs not only significantly improve insulin sensitivity but also may have antiproteinuric effects in genetically obese diabetic rodents and patients with type II diabetes and diabetic nephropathy. Moreover, troglitazone reduced expression of ECM proteins and transforming growth factor-beta in glomeruli from streptozotocin-induced diabetic rats. Many other properties including antiproteinuric, hemodynamic, and antihypertensive effects in insulin-dependent diabetes mellitus suggest that PPAR-gamma ligands might have a direct, beneficial renal effect, independent of their capacity to

improve glucose tolerance. Besides their antidiabetic effects, thiazolidinediones have been shown to lower blood pressure in diabetic patients with hypertension and patients with diabetic nephropathy through multiple mechanisms. Several studies showed the efficacy of PPAR-gamma agonists to ameliorate the progression of glomerulosclerosis. The effect is independent of insulin effects and could only be partially due to lipid effects. These renal protective effects of PPAR-gamma agonists suggest that they may provide a novel intervention strategy to prevent vascular and glomerular sclerosis.

23. PPAR-gamma agonists and diabetic nephropathy

Zhang Y, Guan Y.

Curr Diab Rep 2005 5 (6): 470-5.

Diabetic nephropathy is a clinical syndrome of albuminuria, declining glomerular filtration rate, and increased risk of cardiovascular disease. Multiple mechanisms have been implicated in its pathogenesis. Although current therapies appear to be effective, treatment of diabetic nephropathy remains suboptimal. This review summarizes the recently emerging evidence suggesting that peroxisome proliferator-activated receptor-gamma agonists may prove to be effective therapeutic agents in the treatment of diabetic renal complications.

24. Protective effect of peroxisome proliferator activated receptor gamma antagonists on diabetic and non-diabetic renal diseases

Chung BH, Lim SW, Ahn KO et al.

Nephrology (Carlton) 2005 10 Suppl 2: S40-3.

Summary Peroxisome proliferator activated receptor gamma (PPARgamma) agonists has not only antidiabetic effect but also a protective effect against various types of injury of the kidney. The protective effects of PPARgamma agonists are observed in diabetic nephropathy and non-diabetic renal disease such as 5/6 ablation model of renal failure, experimental glomerulonephritis, ischemia-reperfusion injury, hypertensive nephropathy and cyclosporin-induced renal injury. The mechanism of renoprotection by PPARgamma agonist is multifactorial. Antifibrotic and anti-inflammatory effects, suppression of renin-angiotensin system, vascular protective effect and antiapoptotic effect were proposed.

25. Stem cells and progenitor cells in renal disease

Haller H, de Groot K, Bahlmann F et al.

Kidney Int 2005 68 (5): 1932-6.

Stem cells and progenitor cells are necessary for repair and regeneration of injured renal tissue. Infiltrating or resident stem cells can contribute to the replacement of lost or damaged tissue. However, the regulation of circulating progenitor cells is not well understood. We have analyzed the effects of erythropoietin on circulating progenitor cells and found that low levels of erythropoietin induce mobilization and differentiation of endothelial progenitor cells. In an animal model of 5/6 nephrectomy we could demonstrate that erythropoietin ameliorates tissue injury. Full regeneration of renal tissue demands the existence of stem cells and an adequate local „milieu”, a so-called stem cell niche. We have previously described a stem cell niche in the kidneys of the dogfish, *Squalus acanthus*. Further analysis revealed that in the regenerating zone of the shark kidney, stem cells exist that can be induced by loss of renal tissue to form new glomeruli. Such animal models improve our understanding of stem cell behavior in the kidney and may eventually contribute to novel therapies.

26. Ischemic nephropathy: detection and therapeutic intervention

Garcia-Donaire JA, Alcazar JM.

Kidney Int Suppl 2005 (99): S131-6.

Although the real prevalence of ischemic nephropathy as a cause of end-stage renal disease is unknown, its incidence has increased in past years. The diagnosis of this pathology requires that a number of functional and anatomic tests be carried out. The initial approach should be to perform duplex Doppler ultrasonography which, besides providing data on the size and extent of the stenosis, enables the intrarenal resistive index to be estimated to determine the pattern of renal parenchyma injury and the expected progression if revascularized. The most frequently used morphologic techniques are magnetic resonance angiography and computer tomography angiography. In the event of ischemic nephropathy, it is necessary to perform a renal arteriography regardless of the inherent risks of contrast toxicity or atheroembolism. Various therapeutic options are reviewed, with emphasis on percutaneous transluminal renal angiography plus stent as the first indication. Even though initial reports were contradictory, several meta-analysis have concluded that better blood pressure control and renal function improvement are achieved with percutaneous transluminal renal angiography plus stent than with conventional medical therapy. Surgical revascularization is preferable in patients with severe aorto-iliac pathology and renal artery ostion complete thrombosis. The risk and benefits of these procedures must be evaluated on an individual basis.

27. A randomized, double-blind, placebo-controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome

Cattarelli D, Spandrio M, Gasparoni A et al.

Background Vasomotor nephropathy is a frequently observed renal dysfunction in very preterm neonates. **Objective** To determine whether theophylline could prevent vasomotor nephropathy in very preterm infants with respiratory distress syndrome (RDS). **Methods** Randomized double-blind, placebo controlled trial of 50 preterm infants with gestational age ≤ 32 weeks needing assisted ventilation. Infants received an intravenous dose of theophylline (1 mg/Kg) or placebo for three days. Twenty-four-hours volume was measured daily. On day 2, 5 and 11, blood samples and 12-hours urine collection were analysed for electrolytes, creatinine, urea. **Results** On day 1 urine output was significantly higher in theophylline (2.4 ± 0.9 ml/Kg/h) than in placebo group (1.6 ± 1.0 ml/Kg/h; $P=0.023$); the incidence of oliguria was significantly lower in treated (4.7%) than in placebo group (33%). Twenty-four hours after the first administration of theophylline/placebo, serum creatinine was significantly lower in theophylline (0.76 ± 0.23 mg/dl) than in placebo group (1.0 ± 0.41 mg/dl; $p=0.025$). On day 5 an increase of serum creatinine was observed in both groups. On day 11 a significant reduction of serum creatinine was observed, as compared to day 5, without difference between the two groups. **Conclusions** Our results suggest that in very preterm infants with RDS early theophylline administration improves renal function during the two first days of life.

28. Emerging therapies for polycystic kidney disease

Gattone VH.

Curr Opin Pharmacol 2005 5 (5): 535-42.

Polycystic kidney disease are the most common, monogenetic, inherited disease in humans. Numerous human genes or gene loci are associated with a renal cystic phenotype. Currently, there are no treatments available to slow the development of renal cystic pathology; however, animal studies identified several potential approaches to intervene in the disease process. The most advanced therapy is the use of vasopressin V(2) receptor antagonists, which reduce renal cAMP, a known of renal cystic enlargement. Other therapies under study include the use of c-myc antisense oligonucleotides and epidermal growth factor receptor tyrosine kinase inhibitors. Considering the divers genes that cause renal cysts and the multiorgan involvement of these diseases, multiple therapeutic approaches will eventually be necessary to treat these diseases.

29. The safety and efficacy of ferumxtyol therapy in anemic chronic kidney disease patients

Spinowitz BS, Schwenk MH, Jacobs PM et al.

Kidney Int 2005 68 (4): 1801-7.

Background Administration of safe and effective iron therapy in patients with chronic kidney disease is a time consuming process. This phase II clinical trial studied ferumoxytol, a semi-synthetic carbohydrate-coated iron oxide administered by rapid intravenous injection to anemic chronic kidney disease patients (predialysis or undergoing peritoneal dialysis). **Methods** Inclusion criteria included hemoglobin ≤ 12.5 g/dL and transferrin saturation $\leq 35\%$. Twenty-one adult patients were randomized to receive ferumoxytol in a regimen of 4 doses of 255 mg iron in 2 weeks or 2 doses of 510 mg iron in 1 to 2 weeks. Ferumoxytol was administered at a rate to up to 30 mg iron/sec. **Results** The maximum hemoglobin response following ferumoxytol administration occurred at 6 weeks, increasing from a baseline of 10.4 ± 1.3 g/dL to 11.4 ± 1.2 g/dL ($P < 0.05$). Ferritin increased from baseline of $232 \pm$ ng/mL to a maximum of 931 ± 361 ng/mL at 2 weeks ($P < 0.05$), while the baseline transferrin saturation increased from $21 \pm 10\%$ to $37 \pm 22\%$ at 1 week ($P < 0.05$). Seven adverse events in 5 patients during this trial were deemed possibly related to ferumoxytol, none serious. These events included constipation, chills, tingling, a gastrointestinal viral syndrome, delayed pruritic erythematous rash, and transient pain at the injection site. **Conclusion** Although larger studies are required, this small study demonstrates that ferumoxytol can be safe and effective in increasing iron stores, is associated with an increased hemoglobin response, and is well tolerated at a rapid infusion rate.

30. Clinical observation of ginkgo biloba extract injection in treating early diabetic nephropathy

Lu J, He H.

Chin J Integr Med 2005 11 (3): 226-8.

Objective To observe the effect of Ginkgo biloba extract injection (GB) in treating early diabetic nephropathy (DN). **Methods** Sixty DN patients were divided into two groups, the treated group were treated by GB and Western medicine, and the control group were given Western medicine alone. The study lasted for 4 weeks. Fasting plasma glucose (FPG), blood pressure, 24 h urinary albumin excretion (UAE), endogenous creatinine clearance rate (Ccr), blood lipids and hemorheology indices were examined before and after the study. **Results** Compared with the control group, UAE were significantly decreased ($P < 0.01$); blood lipids and hemorheology indices were all improved after treatment in the treatment group ($P < 0.01$). But in FPG and blood pressure there was no significant change between the treated group and the control group ($P > 0.05$). **Conclusion** GB is effective in treating early DN through decreasing urinary albumin excretion rate, regulating blood lipids, improving renal function and hemorheology.

31. IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients

Shoenfeld Y, Katz U.

Autoimmunity 2005 38 (2): 123-37.

Abstract Intravenous immunoglobulin (IVIg) is used to treat a number of immune-deficiencies and autoimmune diseases. It has been shown that IVIg contains anti-idiotypic antibodies, which explains its immunomodulatory action. In murine models, recent investigations have demonstrated that IVIg can prevent and reduce the affliction by systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and scleroderma. Relevant disease-specific fractions of IVIg were able to reproduce and even enhance the therapeutic effects in a murine model. IVIg treatment before tumor resection in rodents inoculated with melanoma and sarcoma cells dramatically improved the cure rate (50%) in comparison to the control group (0%). In patients affected by SLE, several clinical manifestations responded to IVIg treatment including serositis, hematological manifestations, treatment-resistant nephritis and central nervous system involvement. Similarly, in women with recurrent fetal loss due to APS, IVIg was able to diminish the abortion rate. Vasculitides such as Churg-Strauss's and Wegener's and skin fibrosis in patients affected by scleroderma improved after IVIg treatment. In agreement with in vitro investigation, prolonged survival has been noted in cancer patients treated with IVIg. We suggest that in the presence of steroid and immunosuppressive-resistant autoimmune disease, IVIg is a rational and safe choice.

32. Clinical efficacy of intravenous immunoglobulin for patients with MPO-ANCA-associated rapidly progressive glomerulonephritis.

Ito-Ihara T, Ono T, Nogaki F et al.

Nephron Clin Pract 2005 102 (1): c35-42.

Background To determine whether intravenous immunoglobulin (IVIg) can control disease activity in patients with myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated rapidly progressive glomerulonephritis (RPGN). **Methods** Twelve patients with serologically and histologically confirmed MPO-ANCA-associated RPGN (7 men, 5 women; mean age 71 +/- 3 years) received IVIg (400 mg/kg/day) alone for 5 days. The effects of IVIg were evaluated by white blood cell counts, serum C-reactive protein levels, Birmingham Vasculitis Activity Score, rate of change in reciprocal creatinine (1/Cre), and plasma tumor necrosis factor-alpha levels after IVIg administration. Corticosteroids with or without cyclophosphamide were commenced after IVIg. **Results** After IVIg treatment, a significant decrease was observed in white blood cell count ($p < 0.05$), C-reactive protein values ($p < 0.001$), and Birmingham Vasculitis Activity Score ($p < 0.001$) concomitant with the amelioration of systemic symptoms. The rate of change in 1/Cre significantly improved ($p < 0.05$). Plasma tumor necrosis factor-alpha levels that were significantly elevated in patients before IVIg compared with normal controls ($p < 0.0001$), rapidly declined after IVIg with a significant reduction ($p < 0.05$). Three months post-treatment with IVIg, all patients showed improvement of disease without serious infectious complications. **Conclusion** IVIg is a potential component of remission induction therapy for patients with MPO-ANCA-associated RPGN.

33. Apheresis for MPO-ANCA-associated RPGN-indications and efficacy: Lessons learned from Japan nationwide survey of RPGN

Yamagata K, Hirayama K, Mase K et al.

A national survey concerning rapidly progressive glomerulonephritis (RPGN) was conducted in Japan between 1989 and 2000 and resulted in the registration of 715 patients with RPGN. Among the documented patients, the most frequent primary disease was primary pauci-immune crescentic glomerulonephritis (n = 283), and the second most frequent was microscopic polyangiitis (n = 127). Overall, 370 patients had MPO-ANCA, and 23 patients had PR3-ANCA. We found that both renal and patient survival were significantly worse in patients with MPO-ANCA-associated RPGN than patients with PR3-ANCA. Fifty-three patients received apheresis therapy with various combinations of immunosuppressive regimens. They had higher serum creatinine, higher CRP, and a higher frequency of combined pulmonary involvements as compared to the controls without apheresis therapy. In dialysis-dependent patients, no additional benefit from apheresis therapy was observed. Only pulmonary renal syndrome patients with CRP > 6 mg/dl at presentation showed a slightly better prognosis (patient survival with apheresis; 66.7%, without apheresis; without apheresis; 56.7%). Furthermore, a rapid MPO-ANCA titer reduction was observed in patients treated with apheresis. Patients with MPO-ANCA-associated RPGN were older, and had more chronic and sclerotic lesions than patients with PR3-ANCA-associated RPGN. Based on these findings, we suggest that a lower dose of immunosuppressant should be considered in order to avoid opportunistic infection. In this situation, cytoapheresis is the treatment of choice. Nevertheless, in patients with an aggressive form of RPGN with rapid deterioration of renal function like the PR3-ANCA-associated RPGN, or pulmonary renal syndrome complicated severe inflammation, or relapses with high MPO-ANCA titer, we conclude that apheresis therapy should be considered.

34. Reduction of proteinuria with mycophenolate mofetil in predominantly membranous lupus nephropathy

Karim MY, Pisoni CN, Ferro L et al.

Rheumatology (Oxford) 2005 44 (10): 1317-21.

Introduction Lupus membranous nephropathy (LMN) presents a difficult clinical problem as no particular treatment has been proven to be effective. Studies have shown good results with mycophenolate mofetil (MMF) in proliferative lupus nephropathy (LN) (WHO class III and IV disease). **Objective** To study whether MMF treatment was effective in membranous predominant LN in patients resistant to or intolerant of other immunosuppressive agents. **Patients and Methods** We retrospectively studied 10 patients with systemic lupus erythematosus who had biopsy-proven predominant LMN (six Vc patients and four Va or Vb patients). Previous treatments included cyclophosphamide, azathioprine, ciclosporine and corticosteroids. The following parameters were recorded at baseline and follow-up: blood pressure, ECLAM, proteinuria, serum albumin and creatinine, routine hematology and immunology. **Results** The study included eight women and two men, mean age 38.4 +/- 7.1 yr (range 30-49 yr). The racial distribution was as follows: five Caucasian, and five Black Patients. The mean treatment time with MMF was 18.8 +/- 15.4 months (range 3-52 months). Twenty-hour urinary protein excretion was reduced from median 2.26 g (range 0-7.92 g) to median 0.66 g (range 0.08-3.85 g) at follow-up (P = 0.0039). Serum albumin increased significantly after treatment from median 29.5 g/l (range 14.0-42.0 g/l) to 33.5 g/l (range 23.0-40.0

g/l) at follow-up ($P = 0.04$). There were no significant changes in serum creatinine ($P = 0.55$). Conclusion MMF is a potentially useful immunosuppressive agent in reducing the proteinuria associated with membranous predominant LN.

35. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis

Joy MS, Hogan SL, Jennette C et al.

Nephrol Dial Transplant 2005 20: 2725-32.

Abstract Background The treatment approaches to antineutrophil cytoplasmic autoantibody (ANCA) small vessel vasculitis expose patients to the risks associated with long-term use of corticosteroids and cytotoxic agents. In an effort to explore approaches to minimize risks, we conducted a pilot efficacy and safety study of mycophenolate mofetil (MMF) in the treatment of subjects with nonlife-threatening recurrent or cyclophosphamide-resistant ANCA-vasculitis. Methods MMF was initiated at 500mg orally twice daily and gradually increased to a target dose of 1000mg twice daily for a duration of 24 weeks. Concomittant therapy with corticosteroids was allowed. The Birmingham Vasculitis Activity Score (BVAS) was used to assess disease activity and treatment efficacy. ANCA titres, serum creatinine and adverse events were secondary measures of efficacy and/or toxicity. Results Twelve subjects were enrolled in the study. Treatment with MMF led to an improvement in disease activity as measured by the BVAS at 24 weeks ($P = 0.0013$) and 52 weeks ($P = 0.0044$) as compared to baseline. The BVAS decreased from an average of 9.1 ± 3.5 at baseline (range, 3-17) to an average of 2.8 ± 1.9 (range, 1-6) at 24 weeks and to 2.8 ± 4.3 (range, 0-13) at 52 weeks. Early and sustained reductions in BVAS occurred in subjects initially classified as disease relapses vs those with treatment resistance. Side effect profile was consistent with the mechanism of action and pharmacokinetic disposition of MMF. Conclusions MMF is a reasonable option in the treatment of non-life-threatening recurrent or resistant vasculitis and may obviate the immediate need for recurrent use of cytotoxic agents.

36. Medical decision-making in membranous nephropathy: how to use limited clinical research evidence in patients management

Imai H.

Clin Exp Nephrol 2005 9 (3): 206-11.

Evidence-based medicine (EBM) originally referred to the use of a combination of clinical expertise and research evidence to make medical decisions, while carefully considering the patient's preference. In Japan, however, EBM has been misunderstood as the more abstract pursuit of acquiring research evidence and building medical guidelines. This review aims to summarize the available data regarding therapy for membranous nephropathy (MN), a field in which no consensus has been reached, and to discuss medical decision-making by using a decision tree in several model

cases. In clinical practice, we have to consider both the risks and benefits of treatment. These are evaluated by their therapeutic effect (the rate of improvement, no change, or worsening) and by the patient's quality of life (QOL). This process is compatible with essential concept of EBM.

37. Idiopathic membranous nephropathy: outline and rationale of a treatment strategy

du Buf-Vereijken PW, Branten AJ, Wetzels JF.

Am J Kidney Dis 2005 46 (6): 1012-29.

Idiopathic membranous nephropathy is a common cause of nephrotic syndrome. The treatment of patients with idiopathic membranous nephropathy is heavily debated. Based on literature data and our own experience, we propose a rational treatment strategy. Patients with renal insufficiency (serum creatinine level > 1.5 mg/dL [> 135 micromol/L]) are at greatest risk for the development of end-stage renal disease and should receive immunosuppressive therapy. In patients with normal renal function (serum creatinine < 1.5 mg/dL [< 135 micromol/L]), risk for developing end-stage renal disease can be estimated by measuring urinary excretion of beta2-microglobulin or alpha1-microglobulin G. For low-risk patients, a wait-and-see policy is advised. High-risk patients likely benefit from immunosuppressive therapy. Currently, combination of steroids with chlorambucil or cyclophosphamide are best studied. We prefer cyclophosphamide in view of its fewer side effects. Cyclosporine may be an alternative option in patients with well-preserved renal function, although long-term data are lacking. Other immunosuppressive agents, such as mycophenolate mofetil or rituximab, currently are under study; however, data are insufficient to support their routine use.

38. C1 – C2 point monitoring of low-dose cyclosporin A given as a single daily dose in children with steroid-dependent relapsing nephrotic syndrome

Nakahata T, Tanaka H, Tsugawa K et al.

Clin Nephrol 2005 64 (4): 258-63.

Abstract Aim It has been reported that the pharmacokinetics of cyclosporin A (CsA) in children is different from that in adults. It appears that, in general, pediatric patients metabolize CsA more rapidly than adult patients, necessitating the use of higher dose of the drug in pediatric transplant recipients. In this context, we speculated that single-dose daily administration of low-dose CsA may be associated with a higher peak blood level without associated trough blood level elevation, and thereby yield better results and allow safer use of the than conventional twice daily administration dosing used for the treatment of childhood idiopathic nephrotic syndrome (INS). Methods A total of 10 children with steroid-dependent relapsing INS (9 with biopsy-proven minimal change disease) who showed steroid toxicity were enrolled in the study. The initial daily dose of CsA (Neoral) used was around 2.0 mg/kg, given as a single daily dose before breakfast. The dose was subsequently adjusted to achieve a C1-C2 point blood level between 600 – 800 ng/ml. The dose of the concomitantly administered prednisolone was tapered following the commencement of CsA.

Results The mean daily CsA dosage, the mean C1-C2 point blood level and the mean trough blood level in the subjects were 2.2 ± 0.8 mg/kg, 754 ± 71.9 ng/ml and 42.7 ± 29.2 ng/ml, respectively. At the latest observation, after a mean duration of 17 months (6-24 months) of CsA therapy, the minimum dose of prednisolone required for maintenance of clinical remission and the calculated relapse rate were significantly decreased as compared to the respective pretreatment values (0.52 ± 0.46 mg/kg on alternate days, vs. 0.97 ± 0.63 mg/kg on alternate days, and 0.28 ± 0.32 times per six months, vs. 1.06 ± 0.41 times per six months, respectively, $p = 0.005$). No significant was observed in the mean estimated GFR value as compared to the pretreatment value (183.1 ± 35.4 ml/min/1.73m²) vs 185.4 ± 39.3 ml/min/1.73m²). No evidence of CsA nephrotoxicity was observed, in a repeat renal biopsy performed around 12 months after the commencement of CsA therapy in two patients. **Conclusions** Despite the limitations of the study, our results suggest that administration of low-dose CsA as a single daily dose with C1-C2 point blood level monitoring might be an equally effective and safe and, therefore, more cost-beneficial, protocol for the treatment of steroid-dependent cases of relapsing INS, as conventional twice-daily administration of CsA with trough blood level monitoring. Further to confirm the long-term efficacy and safety of this CsA treatment protocol in larger numbers of patients are, however, needed.

39. Treatment of renal diseases with plasma exchange: a single center experience

Nenov K, Stoyanov A, Paskalev D.

Ther Apher Dial 2005 9 (5): A39.

Over the last decades, plasma exchange (PE) has been applied in the treatment of over 150 different disease including nephrological, hematological, neurological, and rheumatological. Clinical benefit has been demonstrated in only about 40 of them and the best results were achieved in disease with pathogenic autoimmune mechanisms. We used PE most frequently in patients with immune and autoimmune nephropathies aiming to decrease pathologically elevated antibody levels, autoantibodies and immune complexes. PE was applied in 40 patients with chronic glomerulonephritis, 29 patients with lupus nephritis, and 9 patients with Schonlein-Henoch nephritis. After 3 to 4 sessions, continuous immunosuppressive therapy was initiated. Significant reduction of antibody titers and immune complexes was achieved. PE was also applied in 45 plasmacytoma patients with nephropathy to reduce plasma viscosity and slow down the progression of myeloma nephropathy. The result was a significantly reduction of pathological elevated plasma viscosity and a detoxification effect. In our clinic plasma exchange procedures were performed by either centrifugal method with Haemonetics M-30 device or by plasma filtration. An average of 1316 mL plasma was removed during a PE session. For substitution purpose donor plasma and saline solution were used. Clinical remission was achieved in 61.3% of all patients without slowing the progression of renal failure, however.

40. High-dose mizoribine therapy for childhood-onset frequently relapsing steroid-dependent nephrotic syndrome with cyclosporin nephrotoxicity

Ohtomo Y, Fujinaga SI, Takada M et al.

Cyclosporin A (CsA) is an effective treatment for frequently relapsing steroid-dependent nephrotic syndrome (FR-SDNS), but its use can be complicated by renal toxicity and a high incidence of relapses after withdrawal. We report 9 adolescent patients with childhood-onset FR-SDNS who had been treated with long-term CsA that resulted in moderate-to-severe CsA nephropathy (CsAN). They were treated with high-dose (mean: 10.1 mg/kg per day) mizoribine (MZR) in an attempt to allow weaning of CsA and/or steroid therapy, and reduce the frequency of relapses. Seven out of 9 patients were weaned off CsA by 1-year follow up, although in the remaining 2 patients, MZR did not show any beneficial effects. Overall, this high-dose MZR therapy results in significant steroid sparing and reduction in relapse rates in our patients. Our experience shows that high-dose MZR therapy in patients with FR-SDNS who are also CsA-dependent appears to be effective in reducing CsA exposure as well as decreasing the frequency of relapses.

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

Frisch G, Lin J, Rosenstock J et al.

Nephrol Dial Transplant 2005 20: 2139-45.

Abstract Background IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. Up to 40% progress to end-stage renal disease (ESRD) over 10-20 years. Currently, treatment is limited. We studied the use mycophenolate mofetil (MMF) vs placebo in a group of North American IgAN patients at high risk for progression disease. Methods Included were 32 patients aged 18-75 years from multiple centres who had their biopsies read at Columbia and who had at least 1 g of proteinuria per day plus at least two of the following risk factors: (i) male sex; (ii) hypertension > 150/90mmHg or requiring antihypertensive medications; (iii) creatinine clearance, measured by 24h urine collection, < 80 and > 20 ml/min at time enrolment; and (iv) presence of glomerulosclerosis or tubulointerstitial atrophy and fibrosis on renal biopsy. Patients were randomized to either 1 year of MMF, titrated up to a dose of 1000mg bid, or placebo. Total follow-up was 2 years. All patients received angiotensin inhibition medication. The primary outcome was a 50% increase in baseline serum creatinine (SCr). Secondary outcomes were an increase of 0.5mg/dl SCr, ESRD and a 50% reduction in proteinuria. Results The mean baseline SCr was 2.4mg/dl. No statistically significant difference were observed for any outcome. Five of 17 who received MMF vs two of 15 patients in the placebo group reached a 50% increase in SCr (P=0.4). In both groups, all patients who reached the primary outcome also reached ESRD. Ten who received MMF vs seven who received placebo had a 0.5mg/dl increase in SCr (P=0.7). Only three MMF and two placebo patients had a 50% reduction in 24h proteinuria. No serious adverse events occurred in either group. Conclusion No benefit was seen in patients who received MMF in this high risk group, probably reflecting the relatively advanced stage of disease of our population. We conclude that MMF is probably not effective in patients with IgAN who already have moderate renal insufficiency.

42. Lamivudine in hepatitis B-associated membranous nephropathy

Tang S, Lai FM, Lui YH et al.

Kidney Int 2005 68 (4): 1750-8.

Background Although lamivudine is effective for treatment of chronic hepatitis B (HBV) infection, its potential therapeutic impact on HBV-related membranous nephropathy (MN) in adults has not been characterized. **Methods** We treated 10 HbsAg-positive patients with biopsy-proven MN, elevated serum alanine aminotransferase (ALT), and HBV-DNAemia (group 1), and compared their clinical course with 12 patients diagnosed to have HBV infection, elevated serum ALT, and MN in the pre-lamivudine era (group 2). **Results** Baseline demographic and clinical parameters were not differed between 2 groups. In group 1, lamivudine treatment was associated with significant reduction in proteinuria, increase in serum albumin, normalization of ALT levels, and disappearance of circulating HBV-DNA during the first year. Four (40%) and 6 (60%) patients went into complete remission (proteinuria <0.3 g/d) at 6 and 12 months, respectively. In group 2, significant proteinuria persisted during the first year. One (8.3%) and 3 (25%) patients went into remission. Cumulative 3-year renal survival [using end-stage renal disease (ESRD) as primary end point] was 100% in group 1 and 58% in group 2 ($P = 0.024$, log rank test). Blood pressure control reached the target of below 130/85 mm Hg in both groups. Lamivudine was well tolerated and not associated with any adverse events. Hepatic decompensation or malignancy was not observed during follow-up in both groups. **Conclusion** HBV-related MN leads to ESRD in a significant proportion of patients before the advent of antiviral therapy. Lamivudine treatment improves renal outcome in HBV carriers with MN and evidence of liver disease.

43. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes

Farvid MS, Jalali M, Siassi F et al.

Diabetic Care 2005 28 (10): 2458-64.

Objective The present study was designed to assess the effect of magnesium plus zinc, vitamins C plus E, and a combination of these micronutrients on nephropathy indexes in type 2 diabetic patients. **Research Design and Methods** In a randomized, double-blind, placebo-controlled clinical trial, 69 type 2 diabetic patients were randomly divided into four groups, each group receiving one of the following daily supplement for 3 months: group M ($n = 16$), 200 mg Mg and 30 mg Zn; group V ($n = 18$), 200 mg vitamin C and 100 IU vitamin E; group MV ($n = 17$), minerals plus vitamins; and group P ($n = 18$), placebo. Urinary albumin excretion and N-acetyl-beta-d-glucosaminidase activity (NAG) in urine were determined at the beginning and at the end of the trial. Treatment effects were analyzed by general linear modeling. **Results** Results indicate that after 3 months of supplementation, levels of urinary albumin excretion decreased in the V and MV groups ($P = 0.034$ and $P = 0.005$, respectively). Urinary NAG activity did not significantly change in any treatment groups. Levels of systolic, diastolic, and mean blood pressure significantly decreased in the MV group ($P = 0.008$, $P = 0.017$, and $P = 0.009$, respectively). Also, combination of vitamin and mineral

supplementation had a significant effects in decreasing fasting serum glucose ($P = 0.035$) and malondialdehyde concentrations ($P = 0.004$) and in increasing HDL cholesterol and apolipoprotein A1 levels ($P = 0.019$). There was no significant change in the levels of these parameters in the other three groups. Conclusion In conclusion, the results of the present study provide evidence for the effects of vitamins C and E and also combination of magnesium, zinc, and vitamin C and E supplementation on improvement of glomerular but not tubular renal function in type 2 diabetic patients.

44. Ruboxistaurin, a protein kinase C (beta) inhibitor, as an emerging treatment for diabetes microvascular complications

Joy SV, Scates AC, Bearely S et al.

Ann Pharmacother 2005 39 (10): 1693-9.

Objective To review current clinical data regarding the pharmacologic actions of ruboxistaurin (LY333531) mesylate, an inhibitor of protein kinase C (PKC) beta, and its role to potentially reduce the development and/or the progression of diabetic microvascular complications. Data Sources Primary literature was obtained via a MEDLINE search (1966-August 2004) and through of pertinent abstracts and presentations at major meetings. Study Selection and Data Extraction Literature relevant to PKC physiology, the pharmacokinetics of ruboxistaurin, and data evaluating the use of ruboxistaurin in treating diabetic microvascular complications in human and relevant animal models was reviewed. Data synthesis PKC is part of a group of intracellular signaling molecules activated in response to various specific hormonal, neuronal, and growth factor stimuli. Hyperglycemia leads to PKC beta 1 and 2 isoform activation, which experimentally has been shown to contribute to the development and progression of diabetic microvascular complications (retinopathy, nephropathy, neuropathy) through various biochemical mechanisms. Animal and/or human studies using ruboxistaurin mesylate, a novel, highly selective inhibitor of PKC beta, have shown delay in the progression and, in some cases, reversal of diabetic retinopathy, nephropathy, and neuropathy. Conclusions Ruboxistaurin mesylate, by inhibiting excessive activation of certain PKC isoforms, has the potential to reduce the burden of microvascular complications for patients with diabetes.

45. The effect of ruboxistaurin on nephropathy in type 2 diabetes

Tuttle KR, Bakris GL, Toto RD et al.

Diabetes Care 2005 28 (11): 2686-90.

Objective Ruboxistaurin selectively inhibits protein kinase C-beta and ameliorates kidney disease in animal models of diabetes. The purpose of this study was to evaluate the effects of ruboxistaurin on diabetic nephropathy in humans. Research Design and Methods A randomized, double-blind, placebo-controlled, multicenter, pilot study was performed to evaluate the effects of 32 mg/day

ruboxistaurin for 1 year in persons (n = 123) with type 2 diabetes and persistent albuminuria (albumin-to-creatinine ratio [ACR] 200-2.000 mg/g), despite therapy with renin-angiotensin system inhibitors. The primary end point was a change in the ACR. Estimated glomerular filtration rate (eGFR) (four-component equation from the Modification of Diet in Renal Disease study) was also calculated. Results At baseline, urinary ACR was 764 +/- 427 mg/g (means +/- SD), and eGFR was 70 +/- 24 ml/min per 1.73 m². Systolic and diastolic blood pressure were 135 +/- 14 mmHg, respectively. HbA(1c) was 8.0 +/- 1.2%. After 1 year, urinary ACR decreased significantly (-24 +/- 9%) in participants treated with ruboxistaurin (P = 0.020) and nonsignificantly (-9 +/- 11%) in the placebo group (P = 0.430). The ACR-lowering effect of ruboxistaurin appeared by 1 month. EGRF did not decline significantly in the ruboxistaurin group (-2.5 +/- 1.9 ml/min per 1.73 m²) (P = 0.185), whereas the placebo group lost significant eGFR over 1 year (-4.8 +/- 1.8 ml/min per 1.73m²) (P = 0.009). Between-group differences for changes in ACR and eGFR were not statistically significant, but this pilot study was underpowered to determine such differences. Conclusions In persons with type 2 diabetes and nephropathy, treatment with ruboxistaurin reduced albuminuria and maintained eGFR over 1 year. Ruboxistaurin may add benefit to established therapies for diabetic nephropathy.

46. Strategies to prevent contrast nephropathy

Oudemans-van Straaten HM.

Minerva Cardioangiol 2005 53 (5): 445-63.

Contrast nephropathy (CN) is a common cause of iatrogenic acute renal failure. Its incidence rises with the growing use of intra-arterial contrast in older patients for diagnostic and interventional procedures. Aim of the present review is to discuss the mechanisms and risk factors of CN, to summarize the controlled studies evaluating measures for prevention, and to conclude with evidence-based strategies for prevention. Pathophysiological mechanisms of CN are intrarenal vasoconstriction, leading to medullary ischemia, direct cytotoxicity, oxidative tissue damage and apoptosis. Nephro-toxicity is related to osmolality, dose and route of the contrast agent and only occurs in synergy with patient factors, such as previous renal impairment, cardiovascular disease, oxidant stress and the use of certain drugs. CN has impact on morbidity and mortality. In patients at risk, the following measures are recommended: discontinuation of potentially nephrotoxic drugs, treatment of intravascular volume depletion, hydration with sodium-bicarbonate (which seems superior to sodium-chloride), limitation of contrast volume and the use of low-osmolal contrast. Furthermore, if starting the day before is feasible, administered oral N-acetylcysteine, or, with urgent interventions, theophylline 200 mg i.v. (once before the intervention) or high dose ascorbic acid. In patients with combined cardiac and renal insufficiency, periprocedural hemofiltration may be considered; this is the only intervention with proven clinical improvement. Large randomised controlled trials are necessary to show whether pharmacological intervention can improve clinical outcomes.

VI. TRANSPLANTATION

1. Pre-transplant plasma and cellular levels of CD44 correlate with acute renal allograft rejection

Rouschop KMA, Roelofs JTH, Rowshani AT et al.

Nephrol Dial Transplant 2005 (20): 2248-54.

Abstract Background Since CD44 is involved in activation, proliferation, rolling and extravasation of lymphocytes, we hypothesized that it could be involved in the pathophysiology of acute renal allograft rejection. Methods Plasma and peripheral blood mononuclear cells (PBMCs) were collected from patients 24h prior to transplantation and analysed retrospectively. Soluble CD44, interleukin-2 (IL-2R), intracellular adhesion molecule-1 (ICAM-1) and C-reactive protein in plasma were determined by enzyme-linked immunoabsorbent assay (ELISA). Cellular CD44 expression on peripheral lymphocytes was determined by flow cytometric analysis. Results Patients who later developed renal allograft rejection had statistically significantly increased soluble CD44 levels, but not soluble ICAM-1 or CRP in plasma prior to transplantation. In addition, cellular CD44 on T-lymphocytes was decreased 24h prior to transplantation in patients that would reject their allograft, compared with patients without rejection. Additionally, plasma CD44 and other cellular CD44 revealed an inversely proportional correlation. Lipopolysaccharide (LPS)-induced immune activation did not influence plasma or cellular CD44 levels in healthy volunteers, suggesting that more specific factors influence the binding of CD44 on T lymphocytes, leading to increased risk of renal allograft rejection. Conclusion Although the exact mechanisms remain to be elucidated and further research is required, soluble CD44 levels and cellular surface CD44 on T lymphocytes prior to transplantation might be useful as predictive markers for the occurrence of acute rejection.

2. Risk factors associated with the deterioration of renal function after kidney transplantation

Seron D, Fulladosa X, Moreso F.

Kidney Int Suppl 2005 (99): S113-7.

Renal function early after transplantation is associated with a large number of risk factors, including donor age and acute rejection. During the 1990s, donor age increased and the incidence of acute rejection decreased. Renal function between the third and sixth month improved slightly, while renal function deterioration between the third or sixth month and the 12th month improved significantly. This modification coincides with the introduction of mycophenolate mofetil and tacrolimus. The tendency for sustained renal improvement early after transplantation became more evident after the introduction of anti-calcineurin-free regimens. Studies of protocol biopsies have

shown that there is an increase of glomerular volume after transplantation and that a large glomerular volume at 4 months is associated with a better glomerular filtration rate. This adaptation mechanism is impaired in patients with chronic allograft nephropathy or in patients with high cyclosporin levels. Taken together, these data suggest that the steady improvement of renal allograft function may be partly explained by a better glomerular adaptation after transplantation because of the avoidance of the vasoconstrictive effect of anti-calcineurin agents, and a significant decrease in the prevalence of chronic allograft nephropathy early after transplantation.

3. Polyomavirus disease in renal transplantation. Review of pathological findings and diagnostic methods.

Drachenberg CB, Hirsch HH, Ramos E et al.

Hum Pathol 2005 36 (12): 1245-55.

Up to 10% of renal transplant recipients can develop polyomavirus nephropathy (PVN) in the allograft, leading to premature graft failure. Recent studies have shown that early diagnosis of PVN before there is irreversible damage to the kidney can result in marked improvement of outcome with resolution of the infection in a large proportion of patients. Early histopathologic diagnosis is complicated by the subtle beginning of the infection and its multifocal nature. This review presents a comprehensive set of guidelines for the effective clinical use of urine cytology and quantitation of viruria and viremia in conjunction with the renal biopsy findings. The morphological features of PVN are presented with specific emphasis on the patterns of PVN that are based on the histological progression of the disease and that correlate with clinical outcome. Also discussed in the context of their clinical significance are the main virological and epidemiological aspects of the BK, JC, and SV40 polyomavirus infections.

4. Polyomavirus DNA and RNA detection in renal allograft biopsies: results from an European Multicenter Study

Schmid H, Nitschko H, Gerth J et al.

Transplantation 2005 80 (5): 600-4.

Polyomavirus mediated nephropathy is an increasingly recognized complication in renal transplant recipients. In all, 362 renal biopsies from 15 European transplant centers were analyzed for presence of polyomavirus nucleic acid (BK virus [BKV] and JC virus [JCV]). We evaluated 302 biopsies of patients with renal allograft dysfunction, including three with known BKV allograft nephropathy (BKVAN), and 60 native kidney biopsies. BKV DNA was detected in 8 of the 302 (2.6%) biopsies obtained for transplant dysfunction, but in none of the controls. BKV RNA, indicating active viral replication, was found in all BKV DNA positive biopsies available for mRNA expression studies. Retrospective immunohistochemical staining was positive for SV40 large T antigen in all seven evaluated biopsies. BKV DNA and RNA were detected in biopsy tissues from patients with

inconspicuous light microscopy for BKVAN. Further studies will evaluate the potential of intrarenal viral BKV RNA as an early predictor for BKVAN.

5. Tissue viral DNA is associated with chronic allograft nephropathy

Sebekova K, Feber J, Carpenter B et al.

Pediatr Transplant 2005 9 (5): 598-603.

Viral infections post-renal transplant (Tx) impact on outcome. Increased rejection rates and decreased renal function secondary to acute CMV, EBV and HHV-6 infections are well described. However, the clinical significance of a mere presence of these viruses on kidney tissue biopsy remains questionable.

Thirty-six kidney biopsies obtained from 17 renal transplants (five females) and two combined liver-kidney recipients (one female) were retrospectively evaluated. Age at Tx ranged from 1.7 to 17.2 yr (median = 7.4). Biopsies were performed as protocol biopsies or when function deteriorated, between 6 weeks and 11 yr post-Tx (median = 1.2 yr). Immunosuppression included steroids and combination of tacrolimus/cyclosporin, mycophenolate mofetil/azathioprin and induction therapy. Fourteen patients received antiviral prophylaxis (ganciclovir/valganciclovir). Renal tissue was classified according to Banff '97 criteria. Tissue CMV, EBV, HHV-6 and HHV-7 was analyzed by PCR. We used an estimation of GFR from average plasma Cystatin C (CysC) and slopes of 1/CysC to assess renal function. The 16/36 biopsies were positive for one virus; 5/36 biopsies were positive for two viruses. In the infected group, Banff '97 scores interstitial fibrosis (ci) and tubular degeneration/atrophy (ct) were significantly higher ($p < 0.03$ vs. non-infected group for both). The slope of 1/CysC, or the proportion of patients on antiviral prophylaxis, did not differ significantly between two groups. In conclusion, a significant number of kidney biopsies showed PCR positivity for CMV, EBV, HHV-6 and HHV-7. This was associated with a significantly higher Banff score for ci and ct; while renal function was not affected. Further controlled studies are required.

6. TGF-beta1 and the development of chronic graft nephropathy: relative roles of gene, mRNA and protein

Morris-Stiff G

Ann R Coll Surg Engl 2005 87 (5): 326-30.

The exact relationship between transforming growth factor beta-1 (TGFbeta-1) and the development of chronic graft nephropathy remains uncertain; however, it would appear that TGFbeta-1 is up-regulated at the protein and mRNA levels during first year following cadaveric renal transplantation and the effect of 'high producer' gene polymorphisms may also be important. This up-regulation of TGFbeta-1 in plasma may provide a novel, non-invasive means of identifying early fibrotic damage before it becomes clinically apparent thus allowing an opportunity for intervention for grafts that

may otherwise fail.

7. A novel biological assay to detect the active form of TGF-beta in urine to monitor renal allograft rejection

Rogier E, Durrbach A, Abecassis L et al.

Kidney Int 2005 68 (4): 1875-83.

Background Transforming growth factor-beta (TGF-beta) plays an important role in renal fibrosis. Measurement of the concentration of the active form of TGF-beta particularly in urine may help our understanding of the mechanism of chronic allograft nephropathy and could be used as a diagnostic tool. However, TGF-beta release and activation are complex and, consequently, there is currently no accurate way to measure TGF-beta activity. **Methods** TGF-beta-sensitive BL41 cells were stably transfected with a reporter plasmid harboring a synthetic TGF-beta-inducible DNA sequence upstream from the luciferase gene. Cells were incubated with urine samples from normal donors or transplanted recipients with or without patent nephropathy, and the active form of TGF-beta was determined as luciferase activity. **Results** We have established a cell line which expresses luciferase activity in response to active-beta in a dose-dependent manner. Moreover, the use of a histone deacetylase inhibitor greatly increased sensitivity to TGF-beta and also stabilized luciferase inducibility. This test is highly specific to active TGF-beta. Detectable levels of TGF-beta were found in urine from patients with renal dysfunction due to acute or chronic renal allograft rejection ($P < 0.001$), but not in that from patients with stable, correctly functional kidneys. **Conclusion** We describe a highly sensitive and specific assay for active TGF-beta. We also show that, in cases of renal allograft, TGF-beta expression is highly and significantly correlated with acute or chronic rejections.

8. The effects of renal transplantation on peripheral blood dendritic cells

Womer KL, Peng R, Patton PR et al.

Clin Transplant 2005 19 (5): 659-67.

Recent advances allow accurate quantification of peripheral blood (PB) myeloid and plasmacytoid dendritic cell (DC) populations (mDC and pDC, respectively), although the response to renal transplantation (RT) remains unknown. Using flow cytometry, PBDC levels were quantified in patients with end stage renal disease (ESRD) undergoing RT. PBDC levels were significantly reduced in ESRD patients pre-RT compared to healthy controls, with further reduction noted immediately following a hemodialysis session. RT resulted in a dramatic decrease in both subsets, with a greater reduction of pDC. Both subsets levels were significantly lower than in control patients undergoing abdominal surgery without RT. Subgroup analysis revealed significantly greater mDC reduction in RT recipients receiving anti-lymphocyte therapy, with preferential binding of antibody preparation to this subset. Samples from later time points revealed a gradual return of

PBDC levels back to pre-transplant values concurrent with overall reduction of immunosuppression (IS). Finally, PBDC levels were significantly reduced in patients with BK virus nephropathy compared to recipients with stable graft function, despite overall IS. Our findings suggest that PBDC levels reflect the degree of IS in renal allograft recipients. Furthermore, PBDC monitoring may represent a novel strategy to predict important outcomes such as acute rejection, long-term graft loss and infectious complications.

9. Chronic renal allograft dysfunction

Chapman JR, O'Connell PJ, Nankivell BJ.

J Am Soc Nephrol 2005 16 (10): 3015-26.

The major causes of renal transplant loss are death from vascular, malignant or infectious disease, and loss of the allograft from chronic renal dysfunction associated with the development of graft fibrosis and glomerulosclerosis. Chronic allograft nephropathy (CAN) is the histologic description of the fibrosis, vascular and glomerular damage occurring in renal allografts. Clinical programs rely on monitoring change in serum creatinine for identification of patients at risk of CAN, but this change occurs late in the course of the disease, and underestimates the severity of pathologic change. CAN has several causes: ischemia-reperfusion injury, ineffectively or untreated clinical and subclinical rejection, and superimposed calcineurin inhibitor nephrotoxicity, exacerbating pre-existing donor disease. Once established, interstitial fibrosis and arteriolar hyalinosis lead to progressive glomerulosclerosis over the subsequent years. There have been a number of approaches to treatment aimed at reducing the impact of CAN, mostly centered around avoidance of calcineurin inhibitors through their elimination in all, or just selected, patients. These immunosuppression strategies combine corticosteroids with azathioprine or mycophenolate mofetil, and/or sirolimus and everolimus. Late identification of CAN in individual patients has meant that strategies for intervening to prevent chronic renal allograft dysfunction and subsequent graft loss tend to be „too little and far too late”

10. Messenger RNA for FOXP3 in the urine of renal-allograft recipients

Muthukumar T, Dadhania D, Ding R et al.

N Engl J Med 2005 353 (22): 2342-51.

Background The outcome of renal transplantation after an episode of acute rejection is difficult to predict, even with an allograft biopsy. **Methods** We studied urine specimen from 36 subjects with acute rejection, 18 subject with chronic allograft nephropathy, and 29 subjects with normal biopsy results. Levels of messenger RNA (mRNA) for FOXP3, a specification and functional factor for regulatory T lymphocytes, and mRNA for CD25, CD3epsilon, perforin, and 18S ribosomal RNA (rRNA) were measured with kinetic, quantitative polymerase-chain-reaction assay. We examined association of mRNA levels with acute rejection, rejection reversal, and graft failure. **Results**

The log-transformed mean (\pm SE) ratio of FOXP3 mRNA copies to 18S ribosomal RNA copies was higher in urine from the group with acute rejection (3.8 ± 0.5) than in the group with chronic allograft nephropathy (1.3 ± 0.7) or the group with normal biopsy results (1.6 ± 0.4) ($P < 0.001$ by the Kruskal-Wallis test). FOXP3 mRNA levels were inversely correlated with serum creatinine levels measured at the time of biopsy in the acute-rejection group (Spearman's correlation coefficient = -0.38 , $P=0.02$) but not in the group with chronic allograft nephropathy or the group with normal biopsy results. Analyses of receiver-operating-characteristic curves demonstrated that reversal of acute rejection can be predicted with 90 percent sensitivity and 73 percent specificity with use of the optimal identified cutoff for FOXP3 mRNA of 3.46 ($P=0.001$). FOXP3 mRNA levels identified subjects at risk for graft failure within six months after the incident episode of acute rejection (relative risk for the lowest third of FOXP3 mRNA levels, 6; $P=0.02$). none of the other mRNA levels were predictive of reversal of acute rejection or graft failure. Conclusions Measurement of FOXP3 mRNA in urine may offer a noninvasive means of improving the prediction of outcome of acute rejection of renal transplants. -

11. Longitudinal analysis of chronic allograft nephropathy: Clinicopathologic correlations

Chapman JR.

Kidney Int Suppl 2005 (99): S108-12.

Background Loss of the allograft from chronic allograft nephropathy and death of the patients from vascular, malignant, or infective disease are the major problems in renal transplantation today. Protocol biopsy of the long-term kidney has provided new data with which to develop strategies for prevention and treatment of chronic allograft nephropathy. Methods Two series of long-term protocol biopsies are reviewed. In the first, renal biopsies were obtained at time 0, and at 3 months and 12 months, and the recipients of the renal allografts were followed up to 15 years. In the second, the kidneys of recipients of simultaneous pancreas kidney transplants were biopsied annually for 10 years, and the results correlated with clinical events. Results Chronic allograft nephropathy is caused by acute and chronic immune-mediated damage, as well as by chronic calcineurin inhibitor nephrotoxicity. Both immune and nonimmune mechanisms exacerbate pre-existing donor disease and ischemia-reperfusion injury. Established interstitial fibrosis and arteriolar hyalinosis lead to progressive glomerular sclerosis and eventual loss the graft. Conclusion Protocol biopsies have shown that clinical parameter of renal function underestimated the severity of chronic graft damage. Strategies for preventing or treating chronic renal allograft dysfunction and subsequent graft loss must better control rejection and simultaneously avoid nephrotoxicity.

12. Rapamycin for treatment of chronic allograft nephropathy in renal transplant patients

Stallone G, Infante B, Schena A et al.

Chronic allograft nephropathy (CAN) represents the main cause of renal allograft loss after 1 yr of transplantation. Calcineurin inhibitor (CNI) use is associated with increased graft expression of profibrotic cytokines, whereas rapamycin inhibits fibroblast proliferation. The aim of this randomized, prospective, open-label, single-center study was to evaluate the histologic and clinical effect of rapamycin on biopsy-proven CAN. Eighty-four consecutive patients who had biopsy-proven CAN and received a transplant were randomized to receive either a 40% CNI reduction plus mycophenolate mofetil (group 1; 50 patients) or immediate CNI withdrawal and rapamycin introduction with a loading dose 0.1 mg/kg per d and a maintaining dose aiming at trough levels of 6 to 10 ng/ml (group 2; 34 patients). The follow-up period was 24 mo. At the end of follow-up, 25 patients (group 1, 10 patients; group 2, 15 patients) underwent a second biopsy. CAN lesions were graded according to Banff criteria. alpha-Smooth muscle actin (alpha-SMA) protein expression was evaluated in all biopsies as a marker of fibroblast activation. Graft function and Banff grading were superimposable at randomization. Graft survival was significantly better in group 2 ($P = 0.0376$, chi (2) = 4.323). CAN grading worsened significantly in group 1, whereas it remained stable in group 2. After 24 mo, all group 1 biopsies showed an increase of alpha-SMA expression at the interstitial and vascular levels ($P < 0.001$); on the contrary, alpha-SMA expression was dramatically reduced in group 2 biopsies ($P = 0.005$). This study demonstrates that rapamycin introduction/CNI withdrawal improves graft survival and reduces interstitial and vascular alpha-SMA expression, slowing down the progression of allograft injury in patients with CAN.

13. Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure

Waid T, CRAF Study Group.

Clin Transplant 2005 19 (5): 573-80.

Background Chronic allograft failure (CRAF) is the leading cause of graft loss post-renal transplantation. This study evaluated the efficacy and safety of tacrolimus as secondary intervention in cyclosporine-treated kidney transplantation patients with impaired allograft function as indicated by elevated serum creatinine (SCr) levels. **Methods** Patients receiving cyclosporine-based immunosuppression who had an elevated SCr at least 3 months post-renal transplantation were enrolled. Treatment allocation was 2:1 to switch to tacrolimus or continue cyclosporine. This analysis was performed after 2 yr; patients will be followed for an additional 3 yr. **Results** There were 186 enrolled and evaluable patients. On baseline biopsy, 90% of patients had chronic allograft nephropathy. Baseline median SCr was 2.5 mg/dL in both treatment groups. For patients with graft function at month 24, SCr had decreased to 2.3 mg/dL in the tacrolimus-treated patients and increased to 2.6 mg/dL in the cyclosporine-treated patients ($p = 0.001$). Acute rejection in 4.8% of tacrolimus-treated patients and 5.0% of cyclosporine-treated patients during follow-up. Two-year allograft survival was comparable between groups (tacrolimus 69%, cyclosporine 67%; $p = 0.70$). Tacrolimus-treated patients had significantly lower cholesterol and low-density lipoprotein levels and also had fewer new-onset infections. Cardiac conditions developed in significantly fewer tacrolimus-treated patients (5.6%) than cyclosporine-treated patients (24.3%; $p = 0.004$). Glucose levels and the incidence of new-onset diabetes and new-onset hyperglycemia did not differ between treatment groups. **Conclusions** Conversion from cyclosporine to tacrolimus results in improved

renal function and lipid profiles, and significantly fewer cardiovascular events with no differences in the incidence of acute rejection or new-onset hyperglycemia.

14. Adding sirolimus to tacrolimus-based immunosuppression in pediatric renal transplant recipients reduces tacrolimus exposure

Filler G, Womiloju T, Feber J et al.

Am J Transplant 2005 5 (8): 2005-10.

In adult renal recipients, coadministration of tacrolimus (TAC) and sirolimus (SIR) results in reduced exposure to TAC at SIR doses of 2 mg/day. Eight pediatric renal recipients (median age at transplant 2.0 years, range: 1.2-12.9 years) were converted to TAC- and SIR-based immunosuppression as a rescue therapy. All patients had biopsy-proven chronic allograft nephropathy. TAC levels were measured using a commercially available EMIT assay and SIR levels with a newly developed assay based on the LC-MS technology. SIR was started at 0.13 +/- 0.05 mg/kg/day (3.51 +/- 1.26 mg/m²/day) in two divided doses. TAC was given at 0.14 +/- 0.09 mg/kg/day, resulting in a trough level of 6.3 +/- 2.5 ng/mL. After the addition of SIR, the median dose required to keep TAC blood trough concentrations within the target range increased by 71.2% (range: 21.9-245.4%), dose-normalized TAC exposure (AUC) decreased to 67.1% and the dose-normalized C(max), a surrogate for absorption rate, to 53.8% (both geometric means) while terminal half-life (t_{1/2}), a pharmacokinetic parameter characterizing systemic elimination, remained unchanged (p<0.93). Adding SIR to TAC-based immunosuppression in young pediatric renal transplant recipients results in a significant decrease of TAC exposure. TAC trough levels should be monitored frequently.

15. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data

Webster AC, Woodroffe RC, Taylor RS et al.

BMJ 2005 331: 810-4.

Abstract Objective To compare the positive and negative effects of tacrolimus and ciclosporin as initial treatment for renal transplant recipients. Design Systemic review. Data sources and study selection Reports of comparative randomised trials of tacrolimus and ciclosporin identified by searches of Medline, Embase, the Cochrane register of Controlled Trials, the Cochrane Renal Group Specialist Register, and conference proceedings. Data extraction and synthesis Two reviewers assessed trials for eligibility and quality and extracted data independently. Data were synthesised (random effects model) and results expressed as relative risk (RR), with values < 1 favouring tacrolimus. Subgroup analysis and meta-regression were used to examine potential effect modification by differences in trial design and immunosuppressive co-interventions. Results 123 reports from 30 trials (4102 patients) were included. At six months, graft loss was significantly

reduced in tacrolimus treated recipients (RR = 0.56, 95% confidence interval 0.36 to 0.86), and this effect persisted up to three years. The relative reduction in graft loss with tacrolimus diminished with higher concentrations of tacrolimus (P=0.04) but did not vary with ciclosporin formulation (P=0.97) or ciclosporin concentration (P=0.38). At one year, tacrolimus treated patients had less acute rejection (RR=0.69 to 0.79) and less steroid resistant rejection (RR=0.49, 0.37 to 0.64) but more diabetes mellitus requiring insulin (RR=1.86, 1.11 to 3.09), tremor, headache, diarrhoe, dyspepsia, and vomiting. The relative excess of diabetes increased with higher concentrations of tacrolimus (P=0.003). Ciclosporin treated recipients had significantly more constipation and cosmetic side effects. No differences were seen in infection or malignancy. Conclusions Treating 100 recipients with tacrolimus instead of ciclosporin for the first year after transplantation avoids 12 patients having acute rejection and two losing their graft but causes an extra five patients to develop insulin dependent diabetes. Optimal drug choice may vary between patients.

16. No difference in degree of interstitial Sirius red-stained area in serial biopsies from area under concentration-over-curves-guided cyclosporine versus tacrolimus-treated renal transplant recipients at one year

Rowshani AT, Scholten EM, Bemelman F et al.

J Am Soc Nephrol 2005 Nov 23 [Epub ahead of print]

Interstitial fibrosis is the main characteristic of chronic allograft nephropathy and long-term graft failure. Cyclosporin (CsA) is thought to be more fibrogenic than tacrolimus. In a prospective, randomized, multicenter trial using a calcineurin-sparing regimen, renal interstitial volume was compared in CsA- and tacrolimus-treated renal transplant recipients by image analysis of Sirius red (SR)-stained cortical areas in protocol biopsies obtained at 6 mo (n = 94) and 12 mo (n = 97) after transplantation. Immunosuppression consisted of CsA or tacrolimus, CD25 mAb, mycophenolate mofetil, and prednisolone. CsA therapy increased the 6-mo for subclinical rejection. The prevalence of subclinical rejection was 38.8% in the CsA-treated and 15.2% in the tacrolimus-treated patient group (P = 0.012). Strikingly, no difference in the degree of interstitial SR-stained area was detectable between the two treatment groups. In particular, previous subclinical rejection episodes did not influence the degree of interstitial volume. Also, no difference in GFR occurred at 1 yr, when the mean GFR mounted 63 ml/min. No significant differences in the degree of interstitial SR-stained area could be observed at 6 and 12 mo between CsA- and tacrolimus-treated renal transplant recipients. Although CsA-treated patients developed significantly more subclinical rejections at 6 mo, this did not influence the degree of SR-staining or the change in renal function at 1 yr.

17. Long-term results in renal transplant patients with allograft dysfunction after switching from calcineurin inhibitors to sirolimus

Bumbea V, Kamar N, Ribes D et al.

Abstract **Background** Switching from calcineurin inhibitors (CNIs) to sirolimus might improve renal function in chronic renal transplant patients. **Methods** In a prospective study, we assessed long-term efficacy and safety parameters in 43 renal transplant recipients who were switched from a CNI (cyclosporin A, 65%, and tacrolimus, 35%) to sirolimus for either chronic allograft dysfunction (n=38) or recurrent cutaneous cancers (n=5). A kidney biopsy was done in 79% of patients prior to conversion, and showed either chronic allograft nephropathy (n=26) or CNI nephrotoxicity (n=7). Conversion was either abrupt or progressive, with CNI withdrawal over 3 weeks. All patients also received steroids with or without mycophenolate mofetil or azathioprin. Patient data were recorded at baseline (D0), at 1 (D30) and 6 months (D180), and 1, 1.5 and 2 years post-conversion. **Results** After a mean post-conversion follow-up of 24 ± 1.5 months, 58 of patients were still on sirolimus. The survival of intent to treat patients and grafts was 95.3 and 93%, respectively. Overall, there was significant improvement in renal function, creatinine clearance increasing from 49.4 ± 14.9 to 53 ± 16.3 ml/min at D30 ($P=0.01$), and to 54.7 ± 20 ml/min at D180 ($P=0.01$). Thereafter, creatinine clearance was not different from baseline, i.e. 54.7 ± 21.7 , 52.8 ± 20 and 51.7 ± 20.3 ml/min at years 1, 1.5 and 2, respectively. We divided the patients into two groups: responders (n=29), those with an increase in creatinine clearance at 6 months post-conversion compared with D0, and non-responders (n=14), those with a decrease in creatinine clearance at 6 months post-conversion compared with D0. In univariate analysis, factors predictive of response included proteinuria at D0 and the magnitudes of the differences between D30 and D0 for serum creatinine and lactate dehydrogenase. The conversion was associated with (i) significant decreases in serum calcium, phosphorus and uric acid, and haemoglobin levels; (ii) significant increases in serum alkaline phosphatase, total cholesterol, parathyroid hormone, and the number of patients on statin and recombinant erythropoietin therapies; and (iii) the appearance of *de novo* proteinuria of >1 g/day in 28% of patients ($P < 0.0009$), which was > 2 g/day in 12% of the entire cohort. Kidney biopsies in 17 patients 2 years after conversion showed the same Banff scores as observed at baseline. We identified three independent predictive factors for a renal response to the switch: absence of proteinuria, presence of antihypertensive therapy at D0 and serum lactate dehydrogenase level at D30. **Conclusion** Conversion from CNIs to sirolimus in renal transplant patients with chronic allograft nephropathy was associated with improved renal function; however, 33% of the patients developed overt proteinuria.

18. Freedom from graft vessel disease in heart and combined heart- and kidney-transplanted patients treated with tacrolimus-based immunosuppression

Groetzner J, Kaczmarek I, Mueller M et al.

Background In end-stage cardiomyopathy where concomitant chronic renal failure is a contraindication for cardiac transplantation (HTx), simultaneous heart and kidney transplantation (HKTx) may be the only feasible therapeutic option. Due to the increased donor shortage, the clinical outcome of combined HKTx patients on tacrolimus-based immunosuppression was assessed with a group of HTx patients. **Methods** Three hundred forty-nine HTxs, including 13 (4%) combined HKTxs, were performed since 1995. Two hundred twenty-one HTx and all HKTx recipients received tacrolimus-based immunosuppression. Acute rejection episodes (AREs),

infections, renal function and clinical outcome were evaluated. Pre-operative renal diagnoses for HKTx patients included cystic nephropathy (n=4), glomerulonephritis (n=4), cytostatica-induced nephropathy (n=1), chronic rejection after renal transplant (n= 1), reflux nephropathy (n=2) and chronic calcineurin-inhibitor-induced nephropathy after HTx (n=1). Twelve patients (92%) were on hemodialysis pre-operatively, 1 underwent implantation of a left ventricular assist device (LVAD) before HKTx. **Results** After 4.7 +/- 2 years, 92% of HKTx compared with 85% of HTx patients had survived (p = 0.42). Acute cardiac rejection episodes were more frequent in HTx than in HKTx patients (0.04 +/- vs 0.02 +/- 0.04 ARE/100 patients-days; p = 0.07). incidence of infection was compared (0.3 +/- 0.2 vs 0.5 +/- 0.4 infection/100patients day). Freedom from transplant vasculopathy was 100% in the HKTx group compared with 71% in the HTx group after 4 years (p = 0.04). **Conclusions** Tacrolimus-based immunosuppression yields promising long-term results in HKTx and HTx. The incidence of transplant vasculopathy seems to be lower after HKTx than after HTx. If these results are secondary to a protective effect of tacrolimus-induced tolerance or of tolerance-associated co-transplantation they will need to be investigated in prospective multicenter trials.

19. Chronic allograft nephropathy and mycophenolate mofetil introduction in paediatric renal recipients

Kerecuk L, Taylor J, Clark G.

Pediatr Nephrol 2005 Aug 16 [Epub ahead of print]

Mycophenolate mofetil (MMF) introduction with current reduction in calcineurin inhibitors has been shown to be beneficial in chronic allograft nephropathy (CAN) in adults. MMF was introduced to 19 children with CAN 26.3 +/- 5.8 (range 3.1-82.6) months after transplantation. Patients were followed up for a mean of 13.2 +/- 2.9 (range 1.2-51.1) months. The mean initial MMF dose was 660 +/- 56 mg/m(2) per day, increased to 1.042 +/- 73 mg/m(2) per day a year later. Cyclosporin was reduced from 138 +/- 10 mg/m(2) per day at MMF introduction, to 116 +/- 15 mg/m(2) per day at 6 months and 107 +/- 24 mg/m(2) per day at 1 year. Six months prior to MMF introduction GFR deteriorated by -32.7 +/- 7.3 ml/min per 1.73m(2) per year. Six month after the introduction of MMF, GFR improved by +26.2 +/- 7.1 ml/min per 1.73m(2) per year (P < 0.001). The introduction of MMF significantly reduced both the graft rejection rate (P=0.01) and systolic blood pressure (P=0.01), without a significant change in antihypertensive treatment. Haematological parameters did not significantly differ before and after MMF introduction. The introduction of MMF in paediatric renal transplant recipients with CAN may cause a significant improvement in GFR in both the short-term and the long-term and may well have a beneficial effect on systolic pressure. MMF has the potential to enable CNI-sparing protocols to be adopted.

20. Immunosuppressive treatment and progression of histologic lesions in kidney allografts

Morales JM.

Kidney Int Suppl 2005 (99): S124-30.

Renal transplantation is the best therapeutic option for patients with end-stage renal disease. Although short-term results are excellent, long-term graft survival has not improved substantially in recent times. Chronic allograft nephropathy (CAN) and death with a functioning graft are the most important causes of graft loss. Recent evidence shows that nephrotoxicity of calcineurin inhibitors contributes to CAN, and the introduction of non-nephrotoxic drugs such as mycophenolate mofetil (MMF) and mammalian target of rapamycin inhibitors may provide new immunosuppressive strategies to improve long-term results after renal transplantation. MMF decreases the risk of developing chronic allograft failure and is useful for treating established CAN, because it has a beneficial effect on allograft fibrosis. Treatment with sirolimus (SRL), a basic immunosuppressive drug given in association with MMF, may offer better renal function, decrease the prevalence of CAN, and downregulate expression of genes responsible for progression of CAN than treatment with cyclosporine A (CsA). SRL also permits an early elimination of CsA from SRL-CsA-steroid regimens and shows better renal function and improved renal histology without risk of rejection. Notably, this approach improves graft survival at 4 years. Further multicenter studies are needed to determine whether both approaches produce similar results by comparing immunosuppression caused by SRL-based and tacrolimus (TAC)-based treatment. Because TAC is the most commonly used anticalcineurin drug, it is important to compare the effects of steroid-TAC-SRL treatment with and without elimination of TAC. Finally, although caution is needed, the use of non-nephrotoxic immunosuppressive treatment may change the natural history of CAN.

21. Non-immunologic intervention in chronic allograft nephropathy

Arias M, Fernandez-Fresnedo G, Rodrigo E et al.

Kidney Int Suppl 2005 (99): S118-23.

Background Chronic allograft nephropathy is the main cause of late graft loss. It has been suggested that both alloantigen-dependent and alloantigen-independent factors influence the development of progressive transplant failure. The present study analyzed the importance of non-immunologic factors in the progression of kidney disease in transplant patients, with the emphasis on well-established risk factors for progression in native kidneys. **Methods** A retrospective analysis was performed on 485 transplant patients who had functioning kidneys for at least 1 year. We investigated whether the initial presence and subsequent maintenance of proteinuria, hypertension, anemia, hyperlipidemia, and hyperparathyroidism influenced the progression of transplant failure. To analyze the relative effects of these factors, patients were categorized into two groups: group A had a baseline serum creatinine concentration of less than 1.5 mg/dL, and group B had a baseline serum creatinine concentration of 1.5 to 3 mg/dL. **Results** High urine protein excretion was a significant independent risk factor for progression of renal failure (group A: relative risk, 3.73; 95% confidence interval [CI], 2.24-6.21; group B: relative risk, 4.01; 95% CI, 2.51-6.39). Hypertension was also a significant independent risk factor for progression, but the risk was lower than for proteinuria (group A: relative risk, 1.2; 95% CI, 1.04-1.75; group B: relative risk, 1.20; 95% CI, 1.02-2.1). Anemia, hyperlipidemia, and hyperparathyroidism had no influence on the progression of renal failure. **Conclusion** Our results show strong independent relationships between high blood pressure, urine protein excretion, and the relative risk of chronic progression of renal failure, as described for native kidney disease. These factors are potentially modifiable and are therefore attractive targets for therapeutic targets.

22. Cancer incidence after immunosuppressive treatment following kidney transplantation

Andres A.

Crit Rev Oncol Hematol 2005 56 (1): 71-85.

Cancer incidence is increased in renal transplant recipients due to immunosuppressant treatment that should to prevent and treat acute rejection. Use of new very potent immunosuppressants has made it possible to reduce acute rejection incidence and improve renal graft survival, although increase of infections and post-transplant neoplasms have become clearer. On the other hand, renal transplant candidates whor remain on dialysis have a greater prevalence of neoplasms than the age-matched general population, either because the neoplasm was the the cause of their renal failure (multiple myeloma or kidney or urinary tract cancers) or because their renal disease entails a risk for cancer development (acquired cystic disease or analgesic nephropathy). Practically, all de novo neoplasms have a greater incidence in renal transplant patients. Cutaneous neoplasms are the most prevalent in renal transplant recipients and their incidence increases with transplant time. Post-transplant lymphoproliferative diseases are more frequent in patients who receive greater immunosuppression (antithymocyte/antilymphocyte globulin or OKT3) or are infected de novo by Epstein Barr Virus (EBV) through the transplanted kidney. Kaposi's sarcoma has a high incidence in the renal transplanted population, does not appear in the general population, and is related with Human Herpes Virus 8 (HHV-8) infections. The incidence of tumors in non-functioning native kidney is especially high in renal transplant due to the presence of acquired cystic disease or analgesic nephropathy. Gold standards of post-transplant de novo renal neoplasm prevention are modulating immunosuppression and avoiding exposure to sunlight and to different oncogenic viruses (EBV, cytomegalovirus, hepatitis B and C viruses).