Diabetic Nephropathy

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Mechanisms

At a symposium on the development of diabetic nephropathy, Erwin Boëttinger (New York, NY) discussed the molecular pathology of diabetic nephropathy in mice and men, referring to the growing problems of chronic kidney disease (CKD) due to diabetes. The U.S. prevalence of CKD is predicted to increase from ~340,000 persons in 2000 to 660,000 in 2010, with annual cost increasing from ~15 to 30 billion dollars. Diabetes differs from other causes of CKD in its predictability, with well-defined functional progression from hyperfiltration to micro- to macroalbuminuria to renal failure. The morphologic findings of glomerular basement membrane (GBM) thickening, mesangial expansion, arteriolar hyalinosis, glomerulosclerosis, and tubulo-interstitial fibrosis are well recognized. Boëttinger termed the cellular substrate of diabetic nephropathy, however, “much less clear,” with podocyte depletion, which appears to be a reproducible early finding, appearing to be crucial to disease pathogenesis. Podocytes are glomerular epithelial cells essential for glomerular structure and function, surrounding glomerular capillaries and forming foot processes contributing to the filtration barrier and providing structural stabilization.

Podocyte depletion in human diabetic nephropathy may be a genetic trait (independent of diabetes), may be caused by detachment from the basement membrane due to the disease process, or may be caused by apoptosis or necrosis.

In mouse models of type 1 (streptozotocin [STZ]) and type 2 (db/db) diabetes, hyperglycemia predictably leads to development of albuminuria. Podocyte loss is seen after onset of hyperglycemia and precedes the onset of albuminuria, with podocyte apoptosis coinciding with the onset of hyperglycemia, again preceding albuminuria. Endocapillary apoptosis is not observed in these models. In cell culture, there is a dose response between ambient glucose and the degree of podocyte apoptosis, suggesting a mechanism for podocyte loss. This cell type does not appear to be able to undergo postnatal growth; therefore, progressive renal damage may ensue. Some of these studies were presented by Susztak et al. (abstract 21-LB), showing that in both a diabetic mouse model and in vitro in a 30-mmol/l glucose solution, podocytes show increased apoptosis with exposure to elevated glucose levels. In another study assessing mediators of the podocyte abnormalities in diabetes, Dessapt et al. (abstract 52) assessed modulators of podocyte detachment via inhibition of β1 integrin expression, which plays a role in cell adhesion to extracellular matrix substrates. Exposure to 25 mmol/l glucose and cyclic exposure to 20% mechanical stress both decreased β1 integrin expression by ~15%, with both factors acting together additively.

Molecular profiling (1) reveals genes linked to glomerular disease in both type 1 and type 2 models, with mesangial matrix expansion appearing to be associated with decreased hydroxyethylidene dehydrogenase-36β isotype 4, an enzyme involved in estrogen and androgen biogenesis, as well as increased osteopontin, presumably playing a role in mesangial matrix synthesis. The cluster of differentiation (CD) 36 multiligand scavenger receptor, which plays a role in uptake of glycated albumin and oxidized LDL (oxLDL), is expressed on platelets, endothelial cells, macrophages, adipocytes, and smooth and skeletal muscle. It mediates oxLDL-induced apoptosis and appears to be involved in tubular degeneration. CD36 expression is induced by high glucose, is increased in proximal tubules in diabetic nephropathy models, and mediates proximal tubular epithelial apoptosis induced by advanced glycation end products and fatty acids. Thus, glucose may stimulate CD36 expression in proximal tubules, suggesting that glycosuria may upregulate CD36 with increased urinary advanced glycation end products and possibly free fatty acids, subsequently mediating apoptosis of tubular epithelium and the resulting tubular degeneration.

Michael Mauer (Rochester, MN) continued the theme of glomerular versus tubular injury in diabetic nephropathy, discussing structure-function relationships in human type 1 diabetes. Glomerular lesions are not seen at the onset of type 1 diabetes, but extensive mesangial expansion, basement membrane thickening, and impact on the glomerular circulation may occur even without evidence of proteinuria, with subsequent nodular changes and afferent and efferent arteriolar hyalinosis culminating in the Kimmelstiel Wilson nodular lesion. Type 1 diabetes disproportionately leads to an increase in mesangial extracellular matrix in comparison to mesangial cellular elements. The tubular basement membrane is thickened in diabetes, with decreased interstitium. GBM and proximal tubular basement width correlate, despite the discrepancy between glomerular hypertension and presumably normal tubular pressures, particularly early in the disease process. Interstitial extracellular matrix expansion occurs late (as opposed to that of the glomerular mesangium), in association with decreased glomerular filtration rate (GFR) and with decreased capillary cross-sectional area. As one progresses from normoalbuminuria to microalbuminuria to overt proteinuria, GBM width and mesangial fractional volume increase on average, although with a great deal of overlap. Furthermore, there is a significant inverse relationship between GBM width and GFR, again with moderately

Abbreviations: ARB, angiotensin II receptor blocker; AT1, angiotensin II type 1; CKD, chronic kidney disease; CVD, cardiovascular disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; IDNT, Irbesartan Diabetic Nephropathy Trial; NF, nuclear factor; oxLDL, oxidized LDL; PKC, protein kinase C; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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great variability. Multilinear regression analysis suggests that albuminuria is better explained than GFR by glomerular structural changes (2).

Mauer discussed renal biopsy findings in persons with type 1 diabetes, including atubular glomeruli not having egress, of short atrophic tubules with the beginning of the proximal tubule covered with epithelial cells, and long atrophic tubules, all of which are often associated with Kimmelstiel Wilson nodular lesions. In proteinuric patients, only 32% of glomeruli have normal tubular egress. Comparing normo-, micro-, and proteinuric patients, glomerular tubular junction abnormalities are essentially only seen in the latter state, suggesting this to be a late manifestation of diabetic CKD. Using a form of regression analysis, Mauer's analysis suggested a "breakpoint" of histological worsening at an albumin excretion rate of 52 μg/min. The relationship of renal structure and function, then, appears to explain the long silent period followed by clinical nephropathy. Addressing the frequent finding of denuded glomerular podocytes, with 98, 94, 88, and 78% of mesangial GBM covered by intact podocytes in control subjects and normo-, micro-, and macroalbuminuric patients' biopsies, respectively, Mauer noted that the finding of podocyte detachment is more sensitive than that of foot process abnormality for early podocyte injury. He speculated that GBM and mesangial changes in association with progressive podocyte injury ultimately result in proteinuria. Although mesangial expansion accounts for substantial proportion of GFR loss, then, new lesions emerging with proteinuria are important contributors of GFR decline, perhaps explaining some of the renoprotective effects of drugs that lower urinary protein excration.

Hermann Haller (Hanover, Germany) discussed "unexpected relations" that have been found between protein kinase C (PKC) and diabetic nephropathy. Hyperglycemia may increase PKC with a subsequent increase in endothelial cell permeability, a phenomenon that is mediated by phorbol ester, which activates PKC in a number of settings. The recognition of multiple subgroups of PKC isoforms differing with regard to regulatory subunits and intracellular distribution, however, complicates the interpretation of these phenomena. In a STZ-induced diabetic rat model, levels of PKC-α increased, with translocation to the cell membrane, and PKC-ε increased as well. Overexpression of PKC-β leads to increase in transforming growth factor (TGF)-1 and in levels of the TGF-1 receptor. In a mouse not expressing PKC-α with STZ-induced diabetes, the increase in PKC-α does not occur, but increase in renal size and TGF-1 occur in a fashion similar to that in the wild type, suggesting that this PKC isoform cannot mediate all the expression of diabetic changes, although albuminuria was prevented in this model; therefore, PKC-α may mediate the effect of diabetes on permeability, although not that leading to increased matrix formation. Expression of the transmembrane podocyte protein nephrin and that of perlecan are blocked by hyperglycemia in the wild type, but not in animals not expressing PKC-α, and tubular atrophy with increased apoptosis occurs in STZ-induced diabetic mice, is increased by overexpression of PKC-α, and is largely absent in mice not expressing PKC-α, further showing the complex relationships of PKC to renal disease. After Haller's talk, George King (Boston, MA), who has been involved in the development of PKC-β inhibitors, commented that such isoform-specific inhibitors are necessary to develop therapeutic approaches and that it is important not to generalize from one to another tissue or from one to another species, as there is great variability. He noted that mice not expressing PKC-β do show decreased diabetes-related proteinuria. In a presentation further showing the complex interrelationships of PKC and diabetic renal disease, Meier et al. (abstract 55) reported that STZ-induced diabetic mice not expressing PKC-ε have more severe glomerulosclerosis and tubulointerstitial fibrosis, with increased glomerular TGF-β1 and tubulointerstitial fibronectin and collagen IV expression, suggesting that PKC-ε expression, which is increased in the kidney of diabetic mice, may be protective rather than representing an adverse response to hyperglycemia.

Giancarlo Viberti (London, U.K.) discussed the effect of pressure on the diabetic glomerulus. Both cardiovascular disease (CVD) and renal mortality increase when proteinuria is combined with hypertension (3), suggesting that in addition to metabolic there are hemodynamic factors, with flow and pressure, renin and angiotensin, and cytokines playing roles. The diabetic kidney abnormally regulates intraglomerular pressure with imbalance between afferent and efferent arteriolar vasodilation leading to a 20-mmHg increase in glomerular pressure and allowing systemic hypertension to be transmitted to the glomerulus. In human mesangial cells subjected to repeated 10% elongation, fibronectin, collagen IV, and other extracellular matrix proteins are produced, with increased TGF-β1 and TGF-β1 receptor, vascular endothelial growth factor (VEGF), and angiotensin II type 1 (AT1) receptor. The VEGF response to angiotensin II is enhanced, leading to the concept that hemodynamic stress induces cytokines that may in turn increase permeability and sclerosis. The intracellular pathways for stretch-induced fibronectin and TGF-β1 production involve PKC-dependent activation of p38 mitogen-activated protein kinase (4). Viberti showed a study suggesting that expression of GLUT1, the major glucose transporter in mesangial cells, is increased in a salt-sensitive hypertension model with glomerular hypertension, suggesting that increased intracellular glucose may mimic effects of hyperglycemia in mediating adverse renal effects of hypertension (5).

Examining the relationships of among stretch, the renin-angiotensin system, and the podocyte, Viberti noted that there is reduced glomerular nephrin expression in both type 1 and type 2 diabetics and pointed out that this can be corrected by the angiotensin II receptor blocker (ARB) valsartan but not by amloidipine (6). Mechanical stretch modulates VEGF receptor expression in mouse epithelial cells. Podocyte attachment to the GBM is decreased by stretch via decrease in the anchoring molecules B1 integrin, again with prevention by an AT1 receptor blocker. Furthermore, stretch induces monocyte chemotaxis and enhances nuclear factor (NF)κB binding to DNA, while inhibition of NFκB reduces monocyte chemoattractant protein-1 production and the migration of monocytes. Interestingly, rosiglitazone reduces stretch-induced monocyte chemoattractant protein-1 expression and monocyte chemotaxis in human mesangial cells, an effect mediated by inhibition of NFκB binding to DNA. In a study from Viberti's group, Setti et al. (abstract 837) reported that administration of rosiglitazone to STZ-induced diabetic mice, while not re-
ducing glucose or changing blood pressure levels, decreased albuminuria, suggesting that this anti-inflammatory action may have important clinical benefits. Xu et al. (abstract 53) reported that S18886, an antagonist to the thromboxane A2 receptor, decreased renal immunostaining for 3-o-nitrotyrosine, a marker of oxidative stress, as well as decreasing GBM thickening, mesangial expansion, and glomerular and tubular fibrosis in a streptozotocin-induced diabetic animal model not expressing apolipoprotein E, an effect not seen when aspirin was administered to inhibit cyclooxygenase. Zucollo et al. (abstract 641) from the same group further showed evidence that S18886 decreased atherosclerotic lesion formation.

Epidemiologic trends
At a symposium on the epidemiology of diabetes complications, focusing on changing trends over the past decade, Peter Rossing (Gentofte, Denmark) discussed diabetic microvascular complications, noting that there was a report of a progressive decrease in the incidence of nephropathy in Swedish studies. Data from Pittsburgh have shown a decrease in end-stage renal disease, somewhat supporting the Swedish findings. Pima Indian studies, however, show increasing incidence of proteinuria, and Danish data have not shown improvement over the past several decades, perhaps due to poorer glycemic control and more frequent cigarette smoking. The most recent Danish data suggest that with improved antihypertensive therapy, somewhat better glycemic control, and less cigarette smoking, there has been a decrease in proteinuria. A 10-year follow-up study of persons with type 1 diabetes at the Steno Diabetes Center suggests that smoking, poor glycemic control, and high normal urine microalbumin are all risk factors. Rossing noted the DCCT (Diabetes Control and Complications Trial) follow-up findings that those persons in the intensive intervention group who had better glycemic control during the study had persistent decreases in renal disease despite subsequent elevation in glucose to levels similar to those of the control group (7) and pointed out the Steno study showing that multifactorial intervention reduced microvascular events at 4 and 8 years with suggestion of prevention of CKD and visual loss (8). New blindness induced by diabetes has declined in recent years in Swedish studies, with Danish data showing rates of proliferative retinopathy of 31, 30, 19, and 13% in persons with diabetes onset in 1965–1969, 1970–1974, 1975–1979, and 1979–1984, respectively, who were followed for at least 20 years (9). Factors increasing the prevalence of CKD due to diabetic nephropathy include the increasing prevalence of type 2 diabetes, the development of type 2 diabetes at a younger age, better survival, differences in racial susceptibility, and increased availability of dialysis facilities. The number of persons with diabetes is expected to increase markedly in the U.S. over the next 30 years. Survival in persons with diabetic nephropathy has increased from a median of 7 to 14 years in the Danish cohort, leading to an increasing prevalence of such persons. Strategies to reduce CKD would include prevention of type 2 diabetes either by lifestyle change or use of medications, screening for microalbuminuria, and improving blood pressure control with more use of agents affecting the renin-angiotensin system. Worldwide, 42% of persons with diabetes have microalbuminuria, with a particularly high prevalence in Asian diabetic patients. Rossing studied regression to normoalbuminuria in patients with microalbuminuria and found that permanent regression occurred in only 13% of the Danish series, although this could be improved by ACE inhibitor treatment, which decreased progression of normo- to microalbuminuria by 62%. Normal blood pressure was important for this outcome. Persons with CKD having both good glycemic control and well-controlled blood pressure showed a decrease in GFR of 1.5 ml · min⁻¹ · year⁻¹ compared with 6 ml · min⁻¹ · year⁻¹ among those with hyperglycemia and poor control of hypertension. Rossing concluded that nephropathy is reversible, although noting that the increase in prevalence of diabetes will lead to a progressive increase in the numbers of persons with complications; therefore, it is important to reduce the incidence of diabetes, to screen for high-risk patients, to apply aggressive treatment approaches, and to look for new treatments. When asked about combination ACE inhibitor/ARB treatment, he noted that “it seems that the combination . . . is better in reducing blood pressure and urine albumin excretion,” and that studies in persons without diabetes appear to show improvement in outcome, although pointing out that there is still question about whether the combination is better than maximal doses of the individual agents.

ACE inhibitor versus ARB
In a debate on the relative merits of the two treatments, Mark Molich (Chicago, IL) discussed evidence favoring the use of ACE inhibitors, reviewing the progressive increase in prevalence of diabetic nephropathy and our ability to diagnose this at early stages. Progression of microalbuminuria to overt proteinuria in both type 1 and type 2 diabetes occurs in 40–60% of patients over a 5- to 10-year period. In an epidemiologic analysis of the UKPDS (U.K. Prospective Diabetes Study) database, progression from normo- to microalbuminuria occurred at a rate of 2%/year, from micro- to macroalbuminuria at a rate of 2.8%/year, and from macroalbuminuria to CKD (creatinine ≥2 mg/dl) at a rate of 2.3%/year. The annual cardiovascular mortality of those with normo-, micro-, and macroalbuminuria and of those with CKD was 1, 2, 4, and 12%, respectively, suggesting the importance of preventative treatment (10). There is evidence of benefit of control of glycemia (11) and blood pressure (12), with goal levels <130/85 mmHg (13).

The renin-angiotensin-aldosterone system plays an important role in blood pressure regulation, with angiotensin I metabolized to angiotensin II by the proteases chymase and ACE. Angiotensin II action at the AT1 receptor promotes vasconstriction, with additional effects on renal blood flow and glomerular capillary pressure, as well as nonhemodynamic effects including activation of sodium and water reabsorption, aldosterone synthesis, production of TGF-β, extracellular matrix, and plasminogen activator inhibitor-1, as well as activation of macrophages. Molich noted that ACE also promotes bradykinin synthesis, which adds further blood pressure–lowering effects, as shown by comparison of the effects of the ACE inhibitor captopril alone or with the bradykinin (B2) receptor antagonist icatibant, the latter attenuating captopril’s blood pressure–lowering effect (14).

Animal studies by Brenner showed that the ACE inhibitor enalapril decreased proteinuria and glomerular histological
changes (15), leading to the hypothesis that increased glomerular pressure alters glomerular structure, with there now being evidence of endothelial, mesangial, and epithelial injury from exposure to elevated pressures. Subsequent clinical studies demonstrated that enalapril decreased progression from micro- to macroalbuminuria of normotensive type 1 diabetic persons (16), that enalapril had greater efficacy than metoprolol in hypertensive persons with type 1 diabetes and nephropathy (17), and that captopril decreased proteinuria in persons with type 1 diabetes (18). These studies led to the Collaborative Study Group report of 409 type 1 diabetic patients with either biopsyped nephropathy or retinopathy who had CKD, creatinine ≤2.5 mg/dl, and proteinuria >500 mg/day. Those randomized to captopril had a 51% decrease in the rate of doubling of creatinine and in all-cause mortality or requirement for dialysis or transplantation, with the effect exceeding that due to blood pressure lowering (19). Study participants whose entry creatinine exceeded 1.5 mg/dl had a 23-mL/min/1.73 m² decrease in GFR if randomized to captopril but a 37-mL/min/1.73 m² decrease if randomized to placebo. Similarly, a study of persons with type 1 diabetes and microalbuminuria showed a significantly lower fall in creatinine clearance and a lesser increase in albuminuria in those randomized to captopril than in those receiving placebo. Meta-analyses of individual patient data from 12 trials in type 1 diabetes show that ACE inhibitors reduce the likelihood of progression from micro- to macroalbuminuria by 62%, with a greater treatment effect at higher baseline albuminuria levels (20). In studies of normotensive diabetic persons with microalbuminuria, similar stabilization of both albuminuria (21) and GFR has been reported (22), although not all studies have shown ACE inhibitors to stabilize GFR to a greater extent than other agents (23). There is also evidence that the reduction in albuminuria with ACE inhibitors may not be associated with improvements in renal histology (24).

A number of studies have addressed the use of ACE inhibitors in persons with type 2 diabetes. In a 6-year study of 156 normotensive, normoalbuminuric patients, those receiving 10 mg enalapril daily had an increase in urinary albumin from 12 to 16 mg/24 h, with 7% developing microalbuminuria and an 8% mean decrease in GFR, while those receiving placebo showed an increase in urinary albumin from 11 to 27 mg/24 h, with 19% developing microalbuminuria and a 13% decrease in mean GFR (25). In a 1-year study comparing lisinopril with atenolol in 35 hypertensive persons with type 2 diabetes, blood pressure decreased similarly and albuminuria decreased 45% vs. 12%, but the GFR decreased by 12 mL/min/1.73 m²/year in both groups. Furthermore, in the UKPDS substudy of 1,148 hypertensive patients with blood pressure 160/94 mmHg on entry, comparing captopril 25–50 mg twice daily with atenolol 50–100 mg daily, there was no significant difference in either control of blood pressure or progression of albuminuria (26). A study of 3,577 persons with type 2 diabetes >5 years of age randomized to ramipril versus placebo for 4.5 years showed a 76% reduction in development of macroalbuminuria with ACE inhibitor (27).

Molich discussed a recent 12-month study comparing the ACE inhibitor perindopril with the ARB candesartan in hypertensive patients with type 2 diabetes, showing no difference in blood pressure or albuminuria, although a slightly greater improvement in insulin sensitivity and LDL cholesterol was found with perindopril (28). In a cross-over study regarding the addition of the ARB candesartan to ACE inhibitor treatment with 40 mg lisinopril, 40 mg enalapril, 150 mg or captopril daily in 20 persons with microalbuminuria, a 28% reduction in albuminuria was found, suggesting the potential for additive benefit (29).

Although this may simply illustrate the need for multiple drugs in blood pressure treatment, as shown by a recent comparison of the combination of perindopril and indapamide with enalapril alone, the former producing a greater decrease in albuminuria (30), Molich suggested that combinations of ACE inhibitors with ARBs and either of these classes with diuretics may be particularly effective. He described the question of whether the aldosterone antagonists eplerenone and spironolactone might be useful in the treatment of diabetic nephropathy as “particularly interesting.”

Edward Lewis (Chicago, IL) discussed ARB treatment for diabetic nephropathy, reviewing the benefits of ACE inhibitor but noting that there are inconsistent reports of ACE inhibitor benefit in type 2 diabetes with nephropathy. The Collaborative Study showed without question the benefit of ACE inhibitor in persons with type 1 diabetes and nephropathy. He noted that recent data from the USRDS (U.S. Renal Data System) shows that there appears to be a decrease in progression of type 2 diabetes to end-stage renal disease. Comparing ACE inhibitors with other antihypertensive agents in persons with type 2 diabetes and proteinuria, Lewis referred to a study of ramipril in 160 patients with renal disease, suggesting that ACE inhibitors do not have the same benefit in persons with type 2 as in type 1 diabetes. Recent studies suggest that chymase, the alternative pro tease for formation of angiotensin II from angiotensin I, is expressed in renal mesangial and vascular smooth muscle cells, with levels upregulated in diabetic nephropathy, particularly with hypertension (31), suggesting that both ACE and chymase may be of equal importance for angiotensin II–mediated diabetic nephropathy. An in vitro study comparing chymostatin, captopril, and the combination of both showed the latter to maximally decrease angiotensin II, leading Lewis to speculate that that there might be preferential therapeutic advantage to ARB therapy.

Patients enrolled in the Irbesartan Diabetic Nephropathy Trial (IDNT) had type 2 diabetes with advanced glomerulosclerosis. In comparison with those enrolled in the captopril Collaborative Study, the mean age was 59 vs. 35, 30% had CVD (vs. none), and urine protein was 4 vs. 2.5 g. Blood pressure control was similar in the two studies, with mean systolic blood pressure ~140 mmHg and only one-third of patients having systolic blood pressure ≥135 mmHg. The risk of renal progression in IDNT was half as great for those receiving irbesartan as for those receiving amlodipine or placebo. The IDNT and the similar RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study (32) followed ~3,000 persons in total. There was little effect on mortality, and although ~70% of patients had cardiac events over 3.5 years, there was only benefit in decreasing heart failure. Addressing the question of whether ARB treatment is cardioprotective, Lewis noted that the ELITE II trial of losartan versus captopril showed no difference in treatment of
heart failure between ARBs and ACE inhibitors (33). The VAL-HeFT (Valsartan in Heart Failure Trial) trial, in which standard therapy including ACE inhibitors was given, showed valsartan to be advantageous, although not improving mortality but rather decreasing hospitalization, with particular benefit in patients not already treated with both a -blocker and an ACE inhibitor (34). The LIFE study compared losartan with atenolol, showing benefit of losartan with fewer strokes (35) and a reduction in CVD in the diabetic subgroup (36). The VALIANT (Valsartan in Acute Myocardial Infarction Trial) studied valsartan versus captopril in acute myocardial infarction and showed no difference (37). Finally, the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) study of patients with congestive heart failure and reduced left ventricular ejection fraction who were already on ACE inhibitors with the addition of candesartan showed additive benefit in reducing cardiovascular events (38). Lewis concluded that ACE inhibitors are of proven value in type 1 diabetes with nephropathy and that it is unproven that they are equally effective in type 2 diabetes with nephropathy. He characterized ARBs as being renoprotective in type 2 diabetic nephropathy and suggested that the evidence implies that ARBs should be used in type 2 diabetic subjects with nephropathy and ACE inhibitors in type 1 diabetic subjects with nephropathy. (Note: There has recently been question as to whether ARBs may actually increase circulatory in persons with heart failure, but rather decreasing hospitalization, with particular benefit in patients not already treated with both a -blocker and an ACE inhibitor (34). The LIFE study compared losartan with atenolol, showing benefit of losartan with fewer strokes (35) and a reduction in CVD in the diabetic subgroup (36). The VALIANT (Valsartan in Acute Myocardial Infarction Trial) studied valsartan versus captopril in acute myocardial infarction and showed no difference (37). Finally, the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) study of patients with congestive heart failure and reduced left ventricular ejection fraction who were already on ACE inhibitors with the addition of candesartan showed additive benefit in reducing cardiovascular events (38). Lewis concluded that ACE inhibitors are of proven value in type 1 diabetes with nephropathy and that it is unproven that they are equally effective in type 2 diabetes with nephropathy. He characterized ARBs as being renoprotective in type 2 diabetic nephropathy and suggested that the evidence implies that ARBs should be used in type 2 diabetic subjects with nephropathy and ACE inhibitors in type 1 diabetic subjects with nephropathy. (Note: There has recently been question as to whether ARBs may actually increase the incidence of myocardial infarction [39]; therefore, the benefit under certain circumstances in persons with heart failure may not justify terming them “cardio-protective.”)

Clinical studies
Pathogenesis. A number of fascinating additional studies dealing with various clinical aspects of diabetic nephropathy were reported at the ADA meeting. Amin et al. (abstract 241) followed 479 children with type 1 diabetes from time of diagnosis through puberty, with GFR at 5 years' diabetes duration being 167, 139, and 139 mL/min/1.73m² among those who developed microalbuminuria at 10 years, those who were already microalbuminuric at 5 years, and those who had no microalbuminuria at 5 or 10 years. For each 1% increase in HbA₁c, the risk of developing microalbuminuria increased 30%, with glycemic control appearing to be independent of glomerular hyperfiltration in predicting early nephropathy, leading the authors to speculate that treatment before development of microalbuminuria might be appropriate. De Cosmo et al. (abstract 808) reported that insulin resistance was more strongly associated with increased urinary albumin concentration than with HbA₁c and was independent of age, sex, duration of diabetes, and blood pressure level. Mallmann et al. (abstract 824) showed that increased urine albumin excretion was associated with greater waist circumference, further suggesting a relationship between insulin resistance and albuminuria. Lettão et al. (abstract 820) analyzed 24-h blood pressure profiles in 72 persons with type 2 diabetes. Comparing those with albuminuria rates above versus below the median of 5.6 µg/min, mean systolic blood pressure was 137 vs. 125 mmHg, suggesting that even low levels of albuminuria may have adverse consequences. Javor et al. (abstract 816) reported that in a group of 25 persons with generalized lipodystrophic diabetes, 88% had increased urine albumin. Of 18 subjects treated with leptin, 73% showed improvements in proteinuria and in renal pathology.

Anemia. O'Connor et al. (abstract 1,025) studied the prevalence of Hb <12 and <13 g/dl among men and women with diabetes, showing association with low creatinine clearance and with cardiac disease. The prevalence of anemia was 12% among persons with diabetes and HbA₁c <8%, 17% among those aged >65 years, and 21 and 57% among those with mild and moderate renal insufficiency, respectively. McFarlane et al. (abstract 741) analyzed 2,054 diabetic persons with microalbuminuria and normal creatinine clearance, finding that the Hb of those with versus without CVD was 12.9 vs. 13.5 g/dL, with Hb <12 g/dL associated with a 77% increase in CVD prevalence adjusting for age, family history, male sex, BMI, smoking, hypertension, HDL cholesterol, total cholesterol, and HbA₁c. Abdella et al. (abstract 803) reported the erythropoietin concentration to correlate with hemoglobin and creatinine clearance in a study of 161 persons with type 2 diabetes. Coley et al. (abstract 977) found Hb <11 g/dL among 24% of 5,760 persons with diabetes and GFR 20–60 ml/min, with 40, 26, and 20% anemia prevalence among those with GFR 20–29, 30–44, and 45–60 ml/min, although only 5% were treated with erythropoietin.

Therapeutic approaches. Pins and Keenan (abstract 188) administered an enzymatically prepared hydrolyzed whey protein supplement (20 g daily) versus unmodified whey protein to 30 healthy persons with blood pressure 121–155/81–95 mmHg who were not taking any medications. In addition to significant lowering of blood pressure, ACE activity decreased 25% and bradykinin increased 2.46-fold, suggesting that this may offer a nutritional approach to ACE inhibition. Lim et al. (abstract 569) treated 45 type 2 diabetic albuminuric (mean 373 mg/g creatinine) persons with 50 mg losartan versus 20 mg quinapril for 4 weeks in a cross-over trial, showing albuminuria to decrease 127 vs. increase 21 mg/g, respectively. O’Keefe et al. (abstract 491) presented the results of treatment of 1,483 persons with diabetes with left ventricular dysfunction and signs of heart failure after myocardial infarction with the selective aldosterone antagonist eplerenone versus placebo, showing a 17% decrease in cardiovascular mortality that was similar to that in the nondiabetic subgroup. Scheen (abstract 363) presented a meta-analysis of five randomized controlled trials with an ACE inhibitor and four with an ARB in persons without diabetes, showing that, overall, a 22% decrease is seen in the rate of development of new type 2 diabetes in nondiabetic persons with hypertension or congestive heart failure.

Bell et al. (abstract 504) reported a randomized controlled trial of administration of pyridoxamine versus placebo to 128 persons with diabetic nephropathy, showing a 45% decrease in urinary TGF-β1 and in the rate of decrease of creatinine clearance among the subset with type 2 diabetes and baseline serum creatinine ≥1.3 mg/dL. McGill et al. (abstract 581), in a similar study of pyridoxamine administration to persons with mean serum creatinine 1.9 mg/dL, showed lessening in the rate of decline in creatinine clearance with a decrease in urinary TGF-β1.

References
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