Angiotensin II Receptor Blockers and Nephropathy Trials

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This is the first of a series of reports on the American Diabetes Association (ADA) 61st Scientific Sessions held in Philadelphia in June 2001. It covers topics related to angiotensin II receptor blockers (ARBs) and nephropathy.

At a symposium at the 61st Scientific Sessions of the ADA in June 2001, the results of three recent diabetic nephropathy trials with angiotensin II subtype 1 receptor antagonists were presented. Hans-Henrik Parving, Gentofte, Denmark, pointed out that kidney disease develops in 40% of patients with type 2 diabetes, with 23% of patients in Europe and 46% in the U.S. with end-stage renal disease (ESRD) having diabetes. In the latter population, the proportion increases annually by 1.5%. In type 2 diabetes, microalbuminuria is associated with a 5–10% lifetime risk of progression to overt nephropathy, while patients with normoalbuminuria have a 10–20-fold lower risk. In the Irbesartan for Microalbuminuria in Type 2 Diabetes (IRMA) study, 590 patients with 20–200 μg/min albuminuria with normal serum creatinine and with blood pressure (BP) >135/85 mm Hg were randomized to placebo or 150 or 300 mg irbesartan daily for 2 years. The mean age was 58 years; 70% were male; all were Caucasian; baseline BP was 153/90 mm Hg; baseline albuminuria was 55 μg/min; baseline glomerular filtration rate (GFR) was 110 ml/min; and baseline HbA1c was 7.2%.

Patients treated with aspirin in a dose exceeding 325 mg daily were excluded because of the effect on proteinuria and renal function. The mean trough BP (measured 24 h after the last dose of medication) during the study was 145/84, 143/84, and 142/84 mm Hg with placebo and 150 and 300 mg irbesartan daily, respectively. Progression to macroalbuminuria occurred in 15, 10, and 5%, respectively, of the three groups at 2 years, with adjusted risk reduction of 68% with 300 mg and 44% with 150 mg irbesartan daily. Overall, albuminuria increased 9% with placebo and decreased 6 and 46% at 2 years with 150 and 300 mg irbesartan daily, with a trend for albuminuria to increase after 1 year with 150 mg; albuminuria continued to decrease with 300 mg through 2 years. Two patients treated with 150 mg irbesartan developed K >5.5 mEq/L. The GFR decreased to ~100 ml/min with irbesartan 300 mg and remained at 110 ml/min with placebo and 150 mg irbesartan daily. There were 8.7 vs. 4.5% cardiovascular disease (CVD) events with placebo versus 300 mg irbesartan—not a significant difference in view of the relatively small study size.

Parving concluded, “What is the take-home message? If you want to prevent diabetic kidney disease you need screening for microalbuminuria—it is mandatory. When you have documented [that] the patient has microalbuminuria, you start lifelong treatment with agents interfering with the renin-angiotensin system.” When asked how often to check for microalbuminuria once detected, he suggested that assessment should occur approximately every 3 months “for the rest of the patient’s life.”

Barry Brenner, Boston, MA, discussed the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial of 1,513 patients with type 2 diabetes and nephropathy from 250 centers in 29 countries. Losartan had already been shown to be renal protective in animals and to reduce proteinuria (proportional to basal proteinuria levels) in patients with both diabetic and nondiabetic renal disease at the time of initiation of the study. What was not available in 1993 was “hard end point data” in type 2 diabetic subjects with nephropathy that showed losartan could slow the progression of advancing renal disease to nephropathy. The hypothesis was that long-term treatment would increase the time to primary end point, defined as the doubling of serum creatinine, reaching ESRD, or death. The secondary hypotheses were decreased time to first event and decreased CVD mortality. The vast majority of patients entering the trials were treated with multiple BP medications at study onset, with ACE inhibitor (ACEI) or ARB stopped at entry, and another drug (either α- or β-blocker, centrally acting agent, calcium channel blocker [CCBl], or diuretic) substituted to lower the BP to 140/90 mm Hg.

Patients were treated initially with 50 mg losartan or placebo daily, with BP elevation at 4 weeks leading to an increase in dose to 100 mg daily. The study was discontinued 1 year early because of the accumulating evidence that ACEI were shown to be cardioprotective [particularly in the Heart Outcomes Prevention Evaluation (HOPE) substudy of patients with creatinine >1.4 mg/dl (1)] . Thus, 3.4 years of follow-up is available. Patients had onset of diabetes after age 30 years, with urine albumin >300 mg/g creatinine (mean 4 g/day proteinuria), serum creatinine between 1.3 and 3.0 mg/dl (mean 1.9), and HbA1c <12%. Patients with recent myocardial infarction, coronary intervention, or any history of congestive heart failure (CHF) were excluded. Of these patients, 38% were female and 48% were Caucasian; the mean age was 60 years; 27 and 71% of the losartan patients were treated with 50 and 100 mg daily, respectively. The BP fell progressively during the study, from

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Abbreviations: ADA, American Diabetes Association; ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; CVD, cardiovascular disease; eNOS, endothelial nitric oxide synthase; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HOPE, Heart Outcomes Prevention Evaluation; IL-1β, interleukin-1β; IRMA, Irbesartan for Microalbuminuria in Type 2 Diabetes; ITP, inositol 1,4,5-triphosphate; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator–activated receptor; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; STZ, streptozotocin; TNR-α, tumor necrosis factor-α; TNF-αR, TNF-α receptor; VSMC, vascular smooth muscle cell.
Proteinuria was 4 g/24 h, and 160/87 mm Hg; creatinine was 1.7 mg/dl; the baseline age was 59 years; BP was 152/82 vs. 153/82 mm Hg with losartan versus placebo at baseline to 146/78 vs. 150/80, 143/77 vs. 144/77, and 140/74 vs. 142/74 mm Hg at year 1, year 2, and study end point, respectively. The time to doubling of serum creatinine was 198 days with losartan vs. 162 days with placebo, with a 25% reduction in the risk of doubling of serum creatinine. Further comparison of the losartan and placebo groups showed that 21 vs. 20.3% died and 34 vs. 39% progressed to ESRD. The primary end point risk reduction was 16% by intention-to-treat analysis and was 22% in patients who remained on study treatment. Proteinuria decreased 35% with losartan and did not change with placebo. The rate of annual fall in the reciprocal of the serum creatinine was 0.056 vs. 0.069 ml·mg⁻¹·year⁻¹. In view of the lower BP with losartan at 1 year, the data were reanalyzed after adjusting for BP, with the benefit of losartan on doubling of serum creatinine and on ESRD remaining significant.

Over a period of 3.5 years, one case of ESRD was prevented for every 16 patients treated, with losartan decreasing the number of days with ESRD by 32%, at a savings of $5,300 per patient. Other BP treatment included CCB in 87–90%, which showed that CCB treatment did not interfere with the benefits of losartan. Losartan had CVD effects as well, with a significant difference in first hospitalization for CHF in 11.9 vs. 16.7%. There was a decrease of borderline significance in frequency of myocardial infarction.

Lawrence G. Hunsicker, Iowa City, IA, presented the results of the Irbesartan Diabetic Nephropathy Trial (IDNT), comprised of 1,715 patients with type 2 diabetes, proteinuria >900 mg/day, and creatinine between 1.0 and 3.0 mg/dl in women or between 1.2 and 3.0 mg/dl in men. The patients were with hypertension and without recent active CVD and were recruited from 210 clinical centers worldwide. Patients were randomized to 300 mg irbesartan, 10 mg amlodipine, or placebo for a mean of 2.6 years, with the same primary end point as in RENAAL. CVD and renal end points were assessed. The baseline age was 59 years; BP was 160/87 mm Hg; creatinine was 1.7 mg/dl; proteinuria was 4 g/24 h, and ~30% of patients had experienced at least one CVD episode (>6 months before study entry). The BP goal was 135/85 mm Hg in all groups, with actual levels of 140/77 mm Hg with both amlodipine and irbesartan and with significantly higher levels (mean 144/82 mm Hg) with placebo.

Over the period of follow-up, the placebo and amlodipine groups had similar time to primary end point with irbesartan showing a 22% longer time to primary end point and a 33% longer time to doubling of serum creatinine. Thus, over 3 years, to prevent one primary event, one would need to treat 15 patients, and to prevent 1 patient from doubling their serum creatinine, one would need to treat 10 patients. The mean time from doubling of serum creatinine to the development of ESRD was 24 months. There was no difference in all-cause mortality or in a composite CVD end point, and CHF occurred 37% less frequently with irbesartan than with amlodipine and 27% less frequently compared with placebo. An important finding was a significant decrease in nonfatal myocardial infarction with amlodipine but not with irbesartan versus placebo. Adjustment for BP did not change the significant benefits of irbesartan on renal end points, although Hunsicker noted that each 1-mm Hg lowering of BP was associated with a 3% decrease in the rate of progression to renal end points. Proteinuria decreased slightly with amlodipine and placebo but decreased significantly with irbesartan. An early rise in serum creatinine by 30% or more did not occur with irbesartan or amlodipine and occurred once in the placebo group. Hyperkalemia (>6 mEq/l) occurred in 1.9, 0.5, and 0.4% of patients with irbesartan, amlodipine, and placebo. Study medication was stopped in 23, 23, and 25% of patients for cardiovascular indications.

Treatment of 10 microalbuminuric patients in IRMA-2 for 2 years prevented one case of diabetic kidney disease with macroalbuminuria. Based on extrapolating the RENAAL and IRMA-2 studies to the 595,000 patients with a similar degree of kidney disease in the U.S., 35,000–37,500 cases of ESRD would be avoided by treatment with either agent in comparison to not using ARB or ACEI, resulting in a savings of $0.8–1.0 billion/year. Brenner stressed that the frequency of patients reaching ESRD from the point of doubling of serum creatinine was decreased by 30%, implying that “there is no such thing as the creatinine being too high” to start ARB treatment.

In response to a question, Parving stated, “If the patient comes to my office and is untreated, I would start with an ACE inhibitor.” Brenner added that he agreed with initial use of an ACEI but that if a patient had deterioration of renal function, he would “switch—don’t give me this business add on—there’s no data yet!” Hunsicker stated that now “the best data are for the ARBs.” He pointed out that the optimal BP is 125/75 mm Hg, and he noted, “The lower you get your urinary protein, the better, but [if albuminuria does not decrease] don’t lose heart,” as there is evidence that the benefit for renal function is seen even without decrease in proteinuria. Brenner stated that both the ACEI and ARB have relatively shallow dose response curves for BP but that higher doses may have additional renal benefit (as suggested by IRMA-2). When asked about the relative cardioprotective effects of ACEI (based on the HOPE study) versus ARB, Brenner pointed out that the HOPE study did not show significant benefit in CHF, while the RENAAAL and IDRT studies did show this benefit.

Mediators of vasodilation

A theme of BP treatment assessed in a number of studies presented at the ADA meeting is the role of vasodilatory factors. Natali et al. (653-P) and Schofield et al. (668-P) reported that, among patients with type 2 diabetes, those with hypertension have a decrease in the vasodilatory response to intra-arterial acetycholine infusion, similarly suggesting abnormal endothelial-dependent vasodilation, with the latter study showing intact vasoconstrictive response to norepinephrine (abstact numbers refer to the Abstracts of the 61st Annual. Meeting of the American Diabetes Association, Diabetes 50 [Suppl. 2]:1–A649). Potentiation of insulin’s vasodilatory action via nitrous oxide (NO) production may explain intriguing effects of peroxisome proliferator–activated receptor (PPAR)–γ agonists. Grillot et al. (459-P) studied the effect of such an agent, GW 1929, in spontaneous hypertensive rats, with BP lowering seen at 12 h and plateauing at 3 days. Analysis of changes in aortic mRNA showed that phosphatidylinositol 3-kinase (PI3K) and endothelial nitric oxide synthase (eNOS) were significantly upregulated at 6 h. In streptozotocin (STZ)-diabetic animals, both the drug and insulin were required to produce the BP-lowering effect, with an accompanying change in PI3K and eNOS. Donnelly et al. (275-OR) reported that in-
cubation of pulmonary artery endothelial cells with rosiglitazone produced concentration-dependent increases in transendothelial albumin fluxes, which were maximal after 4 h and subsided over 24 h, suggesting a potential acute effect of these agents related to the development of peripheral edema. Iseovnic et al. (1051-P) reported that angiotensin II decreases the vasodilatory response to IGF-1, blocking IGF-1 stimulated PI3K and NOS in rat vascular smooth muscle cells. BP effects of PPAR-γ agonists have been shown in humans. Home et al. (469-P) reported that in addition to its glucose and lipid-lowering actions, farglitazar, a tyrosine-based nonthiazolidinedione PPAR-γ agonist, decreased BP 5/4 and 8/6 mm Hg at 5- and 10-mg doses, respectively, over 4 weeks in 304 patients with type 2 diabetes and hypertension, although 13% of patients developed peripheral edema at the higher dose. Maruyama et al. (503-P) treated 20 patients with type 2 diabetes with pioglitazone 15 mg daily for 12 weeks, showing a 10/4-mm Hg fall in BP, along with a fall in HbA1c of 1.1% and a decrease in triglycerides among those with visceral obesity. Weston et al. (541-P) noted that rosiglitazone was associated with a decrease in both 24-h ambulatory systolic BP and albuminuria among those patients with microalbuminuria at baseline; the two parameters showed a correlation coefficient of 0.875.

Sharma et al. (733-P) showed that transforming growth factor-β (TGF-β) decreases the mesangial cell receptor for inositol 1,4,5-trisphosphate (ITP), a calcium channel which may mediate vascular dysfunction in diabetes, and that angiotensin II–induced calcium mobilization and cell contraction were also decreased by pretreating glomerular vascular smooth muscle cells (VSMCs) with TGF-β. In further assessments, they showed that expression of the ITP receptor was decreased in aortic VSMC from diabetic rats, with normalization by antibodies to TGF-β. Treatment of STZ-diabetic rats with anti–TGF-β antibodies for 2 weeks showed normalization of the decreased aortic contractile response to A2, further suggesting TGF-β to mediate this abnormality. Interleukin-6 (IL-6) increases endothelial permeability and causes mesangial cell growth, with elevated serum and urine levels in patients with diabetes. Cahoon et al. (701-P) showed that tumor necrosis factor-α (TNF-α) increased 4-fold endothelial cell IL-6 secretion, increased 2-fold glycerated human serum albumin, and increased >10-fold the two in combination. Insulin did not affect IL-6 secretion alone but potentiated the effect of both of the other stimuli, whereas 30 mmol/l glucose had no effect on IL-6 in this model.

**Clinical studies**

Wang et al. (884-P) reported data from the 1996 China National Diabetes Prevalence Study of 42,751 men and women from 11 provinces across China. Comparing nonobese individuals and controlling for sex, BMI, and region, diabetes was associated with 3.5- and 1.8-fold increases in risks of hypertension in urban and rural areas, respectively. The association was particularly prominent at the youngest age, with 6- to 10-fold increases in hypertension rates among individuals younger than 35 years, but 1.5- to 3.0-fold greater rates among individuals 65 years or older. Mera et al. (310-PP) reported data from the Cost of Diabetes in Europe-Type 2 (CODE-2) study of 4,189 patients. Independent predictors of quality of life were neuropathy, stroke, heart failure, retinopathy, dialysis, nephropathy, and hypertension, which explained 77% of the variability of a quality of life measure. A number of studies showed BP treatment patterns among patients with diabetes that are only partially satisfactory. Pogach and Hawley (1046-P) reported that 66% of 503,607 U.S. Armed Forces veterans with diabetes had hypertension, with 14% of the subjects receiving no antihypertensive drug and 32% receiving at least three agents; 79.4% received ACEIs or ARBs, 34.1% received β-blockers, and 45% received CCBs. Of 189,581 subjects with BP measurements available, however, the last value exceeded 1,131 patients with diabetes before 1980 and were evaluated between 1986 and 1988 and between 1996 and 1998. During the follow-up period, the prevalence of hypertension increased from 13 to 29%, with 78 and 82% aware of the condition. Fewer than 500 of those with hypertension alone but 2 to 30% of patients with macroalbuminuria, and from 11 to 5% of patients with overt nephropathy; the frequency of CCB use among patients with hypertension increased from 10 to 31% during the same period. Although these usage patterns are showing improvement, they are certainly not optimal.

Cockcroft et al. (604-P) analyzed the relationship among the pulse pressure, the difference between systolic and diastolic BP, and CVD in the Cardiff Diabetes Database of 2,911 patients followed between 1996 and 2000. In total, the patients experienced 574 coronary events, 168 cerebrovascular disease events, and 157 peripheral vascular disease events. Both the pulse pressure and systolic BP were significantly associated with cerebrovascular and peripheral vascular disease events. Age and total and HDL cholesterol were significantly associated with the pulse pressure, which may be a surrogate measure of increased arterial stiffness.

Fernandez-Real et al. (616-P) reported decreased serum concentrations of soluble tumor necrosis factor–α receptor (TNF-αR) in patients with type 2 diabetes, correlating with the degree of insulin sensitivity. TNF-αR increased with an exercise program that also decreased BP levels.

**Antihypertensive treatment approaches**

Alderson and colleagues (696-P,697-P) administered the AGE inhibitor pyridox-
amine to STZ-diabetic and Zucker diabetic fatty (ZDF) rats. The STZ rats showed lower cholesterol and triglyceride levels and a lesser increase in albuminuria, with lesser production of carboxymethyl- and carboxyethyllysine in skin collagen, and the ZDF rats similarly showed decreased triglyceride, BP, and albuminuria levels, with decreased levels of the advanced lipoxidation end-products malondialdehyde-lysine and hydroxynonenal-lysine, though without effect on the underlying insulin resistance. Ninomiya et al. (724-P) administered EF655, a potent inhibitor for AGE formation, to STZ-treated rats, reporting a similar degree of protection against nephropathy to that seen with captopril administration. Henriksen et al. (1113-P) reported that administration of the ARB irbesartan to female insulin-resistant obese Zucker rats increased insulin sensitivity during an oral glucose tolerance test, with a 14% decrease in fasting glucose and an 18% decrease in cardiac mass and with increased insulin-mediated muscle glucose transport. Lane et al. (716-P) treated STZ-diabetic rats with either the ACEI enalapril or the alpha-adrenergic blocker phenoxybenzamine. Both agents lowered BP and showed similar effects on renal TGF-β, with increased mRNA and plasma TGF-β but decreased renal TGF-β protein levels. If combination treatment leads to additive effects, this may prove to be a clinically useful approach. Stratton et al. (793-P) reported the difference in microaneurism count in the U.K. Prospective Diabetes Study trial of intensive BP control. More than five microaneurisms were present in 19, 23, and 29% of patients with tight BP control (144/82) using captopril or atenolol at 1.5, 4.5, and 7.5 years, but more than five episcides were experienced by 18, 34, and 45% of those with less tight BP control (154/87). At 7.5 years, the risk of experiencing more than five microaneurisms in those without retinopathy at baseline was decreased by 36%, and in those with retinopathy at baseline, there was a 27% reduction. There was no difference between captopril and atenolol. Chang et al. (434-P) compared the nephroprotective effects of the ARB losartan and the ACEI perindopril in 49 type 2 diabetic patients with nephropathy treated for 12 months. Urinary albumin decreased similarly from 332.4 to 223.5 mg/g creatinine with losartan and from 316.6 to 207.2 with perindopril. Curtis et al. (298-PP) studied normoalbuminuric diabetic adolescents, 8 and 11 of whom had normal and high night-to-day BP ratios. Those with higher nocturnal BP had hyperfiltration, which normalized with a 20-day course of enalapril treatment at a dosage of 0.1 mg · kg⁻¹ · day⁻¹. Gaetano et al. (709-P) compared the change in GFR in type 2 diabetic patients with microalbuminuria; 34 of these patients were randomized to slow-release nifedipine, with target diastolic BP <85 mm Hg, and 58 were randomized to enalapril, with target diastolic BP <90 mm Hg. The target systolic BP was 140 mm Hg in each group. The GFR decreased similarly from 125 to 118 mm Hg, from 126 to 119 mm Hg, and from 123 to 115 ml · min⁻¹ · 1.73 m⁻². Albuminuria increased by >50% during follow-up in 53 vs. 29 vs. 19% of the three groups. The increase with enalapril was significantly smaller than that with nifedipine with the lower glyceamic goal. An interesting observation was that those whose mean HbA₁c was >7.5% had a decline in GFR of 7.5 ml · min⁻¹ · 1.73 m⁻² per year, significantly more than the decrease of 1.6 ml/min in those with HbA₁c >7.5%. De Valk et al. (438-P) followed 867 patients with type 2 diabetes and HbA₁c <7%; the HbA₁c level had increased to >7% per period of 2 years in 172 patients. In addition, 9.3% of patients treated with a thiazide or loop diuretics when not administered in combination with an ACEI or distal diuretic, but 4% of the remaining patients showed worsening HbA₁c, suggesting untoward effects of this treatment. Trowbridge et al. (410-P) randomized 38 patients to either self-titration or to dose adjustment by their physicians of antihypertensive medication, showing a 13±7-mm Hg lower home BP with self-titration, but no change in BP measured in clinic, which was consistently at least 10/8 mm Hg higher than the level measured at home. The role of BP measurement at home in aiding treatment deserves further assessment. **Obesity and hypertension** Obesity showed important associations with both hypertension and diabetes in a number of studies. Hill Golden et al. (873-P) reported on 941 white medical students, of whom 41 developed type 2 diabetes after age 50 years and during up to 50 years of follow-up. BP measured in young adulthood in medical school was 124/78 in those who developed diabetes and 119/76 mm Hg in those who did not develop diabetes; this discrepancy is primarily because of greater BMI in those who subsequently developed diabetes. Fineberg et al. (891-P) reported on a 22-year follow-up of 275 individuals. Those now with diabetes had higher systolic and diastolic BP, although this is explained by greater baseline age and BMI. BMI was not correlated with the development of microalbuminuria, but both BP and the development of diabetes were. Murphy et al. (993-P) studied 16 monozygotic and 19 dizygotic twin pairs. Among monozygotic twins, there was greater correlation between, particularly, systolic BP and fasting insulin and between diastolic and systolic BP and birthweight. **Clinical aspects of diabetic nephropathy** Luiza et al. (703-P) biopsied the kidneys of 125 patients with type 1 diabetes whose mean age was 38 years, whose diabetes duration was 23 years, and whose HbA₁c was 8.5%. The factional mesangial volume and glomerular basement membrane width were predictive of the degree of albuminuria, but with considerable overlap of histologic findings between those with normal urine albumin, microalbuminuria, and macroalbuminuria. Sekiguchi et al. (732-P) reported the use of an assay of monocyte protein kinase Cβ activity, which was increased in patients with diabetes and decreased in animal models with insulin treatment or with administration of the inhibitor LY333531. Levels were higher in patients with macroalbuminuria than in those with microalbuminuria, and were higher in patients with retinopathy than those without retinopathy. In follow-up after the Diabetes Control and Complications Trial, Steffes et al. (254-OR) reported that although both the original intensive and conventional treatment groups showed increase in mean HbA₁c to 8.1% at 6 years, the risks of developing micro- and macroalbuminuria were reduced 69 and 87%, respectively, in the group originally receiving intensive treatment, with a trend to decreased hyperglycemia. Roman et al. (726-P) mea-
sured the mean of 12 2-h postprandial glucose levels and 6 fasting glucose levels in 84 patients at 6-month intervals during a 4-year period, showing that the postprandial glucose level, but not the fasting glucose level, was related to change in GFR. Santilli et al. (731-P) treated 17 adolescents with type 1 diabetes, 14 of whom were normoalbuminuric, in a crossover study with a 3-month washout period between interventions. A 3-month period of enalapril treatment did not change in HbA1c and increased TGF-β from 19 to 30 ng/day without change in IGF-1. Intensive diabetic management for 3 months decreased HbA1c 2.5%, with a fall in TGF-β from 21 to 13 ng/day and a decrease in IGF-1 from 476 to 375 ng/day, suggesting that improved glycemic control may have a greater effect than ACEI on renal growth factors in early diabetic nephropathy.

Ferreira et al. (371-P) assessed glucose tolerance among 1,280 Japanese-Brazilians (mean age ~30 years) who participated in a population-based prevalence study of diabetes. Urine albumin levels were >17 mg/g creatinine in 41% of those with diabetes and in 23% of those without diabetes. Microalbuminuria was associated with 1.8-, 2.1-, and 2.9-fold increases in prevalence of central obesity, hypertension, and glucose intolerance. Trevisan et al. (735-P) found that 24-h mean BP was 7.4 mm Hg higher with a 250-mEq sodium diet than with a 200-mEq sodium diet in 20 type 2 diabetic patients with microalbuminuria. The BP was not higher on the high sodium diet in 21 patients without microalbuminuria. There was a 1.9% vs. 0.6% weight gain, and an increase in urine albumin from 80 to 101 vs. from 8 to 11 μg/min in the microalbuminuric vs. the normoalbuminuric group. The microalbuminuric patients had greater insulin resistance measured with a euglycemic insulin clamp and increased glomerular pressure. Amin et al. (698-P) assessed adolescent girls with type 1 diabetes who did versus did not develop microalbuminuria over 10 years of follow-up. Before development of microalbuminuria, free IGF-1 was 1,767 vs. 1,989 ng/ml, free IGF-2 was 1,874 vs. 2,145 ng/ml, testosterone was 1.41 vs. 1.21 mmol/l, leptin was 8.7 vs. 9.8 ng/ml, and HbA1c was 10.9 vs. 9.9%. They speculated that relative insulin deficiency decreases IGF levels, leading to increased growth hormone secretion, which may act with higher free testosterone in causing renal pathology.

**Genetic factors in diabetic nephropathy**

Orchard et al. (727-P) followed 485 type 1 diabetic patients for 10 years; 56 patients had developed overt nephropathy. The estimated glucose disposal rate and total white cell count were multivariate predictors, suggesting roles of insulin resistance and of inflammation. Two genetic polymorphisms related to lipids, the presence of the lipoprotein lipase HING III genotype was present in 37% of patients with nephropathy but 19 of 55 patients homozygous for the haptoglobin 1 allele, 19 of 55 patients homozygous for haptoglobin 2 and 10 of 37 heterozygote patients, showed increased urine albumin levels, with macroalbuminuria in 0, 12, and 3, respectively, suggesting this to be an important susceptibility gene for the development of diabetic nephropathy. Hosoi et al. (629-P), however, showed that haptoglobin polymorphism was not predictive of coronary artery calcification measured by electron beam computed tomography in 158 patients with diabetes. There was an association of coronary artery calcification with the T allele of the methylenetetrahydrofolate reductase gene, which regulates plasma homocysteine levels.

**References**