

Diabetic Nephropathy

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This is the eighth in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, Chicago, Illinois, that discuss aspects of diabetic nephropathy.

Diabetes is the major cause of end-stage renal disease (ESRD) both in the U.S. and around the world. Robert Toto (Dallas, TX) discussed evidence that proteinuria reduction may lead to improved outcome of chronic kidney disease (CKD), pointing out that with aggressive treatment many persons who at one time would have been expected to require dialysis can remain stable. Evidence suggesting that the incidence of ESRD is decreasing among diabetic persons supports Toto's insight.

Rates of decline in glomerular filtration rate (GFR) exceeding that of normal aging ($<1 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$) are associated with adverse outcome. In persons with proteinuric kidney disease, the level of proteinuria appears to be a strong marker predicting the rate of decline in GFR. Given the greater likelihood that the person with proteinuria will progress to renal failure, aggressive treatment of this group, emphasizing blood pressure reduction with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs), is particularly helpful. Mechanisms of albu-

minuria involve abnormalities of the glomerular endothelial barrier, causing excessive filtration, as well as reduction of renal tubular cell albumin degradation and reabsorption. Glomerular hypertension, inflammation, and oxidative stress worsen albuminuria, with angiotensin II and mechanical stress factors contributing to these processes. Both immunoreactive and nonimmunoreactive albumin are present in the urine, the latter representing proximal tubular cell lysosomal enzymatic breakdown. In a study presented at the ADA meeting, Rosolowsky et al. (abstract 221) measured both immunoreactive and total urinary albumin excretion in 444 type 1 diabetic persons, finding increased urinary albumin excretion to predominantly involve the intact molecule, suggesting abnormality of both glomerular and tubular function to occur in diabetic nephropathy. (Abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007.)

Toto reviewed evidence that CKD stabilization and, under certain circumstances, improvement may occur. In animal models of progressive glomerular scarring, the process is reduced with ACEI treatment. Type 1 diabetic patients undergoing pancreas transplantation show improvement in nodular sclerosis beginning after 5 years, with even greater evidence of benefit at 10 years (1). Toto's clinic has treated several hundred persons with such an approach, finding stabilization of CKD. He emphasized the importance of measuring GFR regularly. Multifactorial treatment of CKD includes blood pressure reduction to $<130/80$ mmHg, ACEI/ARB treatment, lowering albuminuria, glycemic control, treatment of anemia, aggressive lipid treatment, treatment of secondary hyperparathyroidism, cigarette discontinuation, weight loss, and exercise.

Several studies presented at the ADA meeting addressed related concepts. Rauseo et al. (abstract 749) studied 728 type 2 diabetic patients, 216 with elevated urine albumin, and found that albuminuria correlated independently with pulse pressure, as well as with diabetes duration and A1C. Similarly, in a study of the development of reduced GFR, Streja et al. (abstract 1,185) found that more intensive management of glycemia among 121 type 2 diabetic people treated for 8 years was associated with a reduction in the rapidity of fall in GFR. Higher levels of A1C and nonsteroidal antiinflammatory use were associated with greater decline in renal function. Bash et al. (abstract 347) followed 1,894 diabetic persons for 6 years, finding that those in the second quartile (A1C 5.5–6.5%), third quartile (A1C 6–5.8%), and highest quartile of A1C ($>8\%$) were 1.2-, 2.1-, and 4.0-fold more likely to have GFR decline to $<60 \text{ ml/min per } 1.73 \text{ m}^2$ than were those in the lowest A1C quartile, with adjustment for age, race, sex, baseline GFR, BMI, blood pressure, coronary disease, smoking, and lipid levels. Onyemere et al. (abstracts 219 and 775) reported 18-month follow-up of 4,301 diabetic patients, using the Modification of Diet in Renal Disease (MDRD) equation to estimate GFR. They found GFR decline of 3.7 vs. 0.5 ml/min per 1.73 m^2 per year in those with GFR $<60 \text{ ml/min per } 1.73 \text{ m}^2$ versus those GFR $>60 \text{ ml/min per } 1.73 \text{ m}^2$. Macroalbuminuria and retinopathy were risk factors for greater decline in GFR in the overall group, with additional risk associated with hypertension and dyslipidemia in those with baseline GFR $<60 \text{ ml/min per } 1.73 \text{ m}^2$. GFR was $<60 \text{ ml/min per } 1.73 \text{ m}^2$ in 13% of those with normoalbuminuria, 22% of those with microalbuminuria, and 48% of those with macroalbuminuria, with diabetes duration, hypertension, coronary disease, and retinopathy found to be risk factors for GFR $<60 \text{ ml/min per } 1.73 \text{ m}^2$ in the latter two groups. There are undoubtedly genetic factors related to CKD development as well. Kateb et al. (abstract 348) reported a relationship between a number of polymorphisms of the superoxide dismutase 1 gene and risks of macro- and microalbuminuria among type 1 diabetic participants in the Diabetes Control and Complications Trial, suggesting that ge-

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; EPC, endothelial progenitor cell; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NO, nitric oxide; PKC, protein kinase C; TGF, transforming growth factor.

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netic variants in the propensity to oxidative injury may be related to development of diabetic nephropathy.

Of interest, CKD is associated with risk of development of diabetes. Lorenzo et al. (abstract 928) followed 856 nondiabetic persons with normal urinary albumin, finding that the development of glomerular filtration rate <60 ml/min per 1.73 m² was associated with increased fasting insulin, triglycerides, free fatty acids, and uric acid and with antihypertensive treatment, but not with waist circumference, controlling for age, sex, ethnicity, blood pressure, glucose, and C-reactive protein (CRP). Donahue et al. (abstract 912) compared 91 persons whose fasting blood glucose increased from <100 to >100 mg/dl during a 3- to 8-year period of observation with 30 control subjects, finding that persons in the upper quintile of cystatin-C were 3.4-fold more likely than those in the lower three quintiles to progress to pre-diabetes, controlling for urinary albumin-to-creatinine ratio, age, baseline glucose level, HOMA-IR, BMI, hypertension, serum creatinine, cigarette smoking, CRP, interleukin-6, and endothelial function markers including E-selectin and soluble intracellular adhesion molecule levels.

Toto emphasized early intervention in discussing therapy of diabetic patients with normo- or microalbuminuria. Several approaches to optimizing inhibition of the renin-angiotensin-aldosterone system were presented at the ADA meeting. Bakris et al. (abstract 601) studied 687 type 2 diabetic persons with chronic kidney disease and macroproteinuria treated for a 52 week period, finding proteinuria to be decreased 27, 29, and 30% in the first, second, and third A1C tertiles among those receiving the angiotensin receptor blocker telmisartan 80 mg daily, but 15, 23, and 23% among those receiving losartan 100 mg daily, without difference in blood pressure or effect of baseline A1C. Taylor et al. (abstract 483) analyzed treatment of 1,417 hypertensive diabetic persons with the direct renin inhibitor aliskiren, finding mean placebo-adjusted 7 and 9/6 and 7 mmHg reductions in systolic/diastolic blood pressure with 150 mg and 300 mg daily dosages, respectively. Elevation in serum potassium and creatinine were seen in two and 1% of patients in this monotherapy study, respectively, although the more important question will be the frequencies of these complications when aliskirin is added to currently used inhib-

itors of the renin-angiotensin-aldosterone system.

In addition to ACEI/ARB treatment, Toto mentioned several approaches being studied, including transforming growth factor (TGF)- β antibodies and vitamin D receptor agonists. Several studies addressing potential approaches to nephropathy prevention and treatment were presented at the ADA meeting. Imai et al. (abstract 768) compared the albuminuria-reducing mechanisms of pioglitazone with those of losartan in streptozotocin-diabetic mice, the former agent normalizing glomerular size and levels of the inflammatory markers ICAM-1 and MCP-1, suggesting an effect on mesangial expansion, while losartan improved the shortening and thinning of podocyte projections in the glomerular capillary bed, suggesting a hemodynamic effect. In clinical analysis of pioglitazone use in persons with CKD, Schneider et al. (abstract 670) and Erdmann et al. (abstract 671) analyzed GFR data from the PROactive study of 5,238 type 2 diabetic patients with type 2 diabetes who had evidence of macrovascular disease, finding 12% with MDRD GFR <60 ml/min/ 1.73 m². These patients had 65% greater incidence of death, myocardial infarction, and stroke, supporting the concept that CKD is a risk factor even among high-risk populations. The CVD events occurred in 21 and 15% of those receiving placebo and pioglitazone, respectively, suggesting benefit of use of this agent. This study was recently published; GFR was calculated from the MDRD formula. Interestingly, more than half of the 597 study participants with GFR <60 were treated with metformin (2), suggesting that many at-risk diabetic persons have renal insufficiency that is not appreciated by treating physicians.

Lee et al. (abstract 779) administered resveratrol, a polyphenol found in many plant species with antiinflammatory action felt to mediate putative benefits of wine ingestion, to streptozotocin-diabetic mice, showing a 50% reduction in diabetes-related renal hypertrophy. There may be benefit of fish oil. Lee et al. (abstract 986) found that among 223 persons with diabetes, those in the highest tertile of fish consumption were 71% less likely to have urinary albumin-creatinine ratio >2.5 mg/mmol. 9,535 persons without diabetes failed to show an association between albuminuria and fish consumption. Wijnhoven et al. (abstract 769) measured heparan sulfate proteoglycans in biopsy

specimens of five normal and 14 diabetic persons, showing reductions in the glomerular basement membrane, with immunohistochemical analysis suggesting that this reduction reflects increased degradation levels, with evidence of increased heparanase expression. Lewis et al. (abstract 573) presented findings of a study of 130 diabetic persons with microalbuminuria receiving maximal ACEI or ARB, randomized to placebo or to the glycosaminoglycan sulodexide, an oral heparinoid which lowers urinary albumin excretion in animal models of diabetic nephropathy. At six months, and two months after subsequent cessation of treatment, respectively, 15 and 12% of those receiving placebo, 33 and 32% of those receiving sulodexide 200 mg, and 18 and 19% of those receiving sulodexide 400 mg daily had either a 50% reduction or normalization of urinary albumin, the 8-month effect of the 200 mg dose statistically significant.

An important series of presentations at the ADA meetings discussed approaches to the accurate assessment of renal function, crucial to the treatment of CKD. It appears that GFR estimates based on serum creatinine, the Cockcroft-Gault (CG) and MDRD formulas, are not optimal, with measurement of serum levels of the cysteine proteinase inhibitor cystatin C appearing to offer a better approach. Perkins et al. (abstract 220) used the reciprocal of the serum cystatin C level as a measure of glomerular filtration rate (GFR), noting this to be particularly useful in the high and normal range of GFR, where the MDRD equation is not accurately able to detect changes. Of 267 and 301 normo- and microalbuminuric type 1 diabetic persons followed for 10–14 years, renal function decline was seen in nine and 31%, respectively, with decline in renal function occurring as early as the development of microalbuminuria was noticed, suggesting that measurement of cystatin C will allow appreciation of early renal function worsening among type 1 diabetic persons. Among microalbuminuric patients, those whose albuminuria regressed, remained stable, and progressed, respectively, showed 16, 32, and 68% likelihood of progressive renal function decline. Age >35 years and A1C $>9\%$ were further risk markers. Premaratne et al. (abstract 224) compared cystatin C, serum creatinine, CG, and MDRD in 4 and 6 variable versions with isotopic ^{99m}Tc-DTPA plasma clearance for GFR assessment in 85 type 1 diabetic persons

NEWS FROM THE FOOD AND DRUG ADMINISTRATION

From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.

The FDA has just issued, in draft form, a set of guidelines on the development of therapies for treating type 1 and type 2 diabetes (and for their prevention). Of note is the new recommendation that long-term safety studies may be required for some therapeutic agents and that as part of the plan for approval of new drugs, “long-term cardiovascular [outcome] studies post-approval [be carried out] in an established time frame.” Specific recommendations are given for preclinical study of peroxisome proliferator-activated receptor- γ agonists and insulin analogs to address potential adverse growth-promoting effects. The guidance document further comments, “Even though HbA1c is appropriate as a surrogate endpoint in many study designs, documented improvement in a serious morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive evidence of benefit for drugs in which substantial safety issues or questions arise.” Thus, the prior supposition that glycemic benefit would clarify the usefulness of a proposed therapy may not now be considered sufficient. Improvement in insulin sensitivity is specifically noted not to be a rationale for approval, while lipid- and blood pressure-lowering effects are suggested as definitely being of importance. Thus, a treatment for metabolic syndrome “ideally should normalize or improve all components of the syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality.” The development of agents associated with weight loss and with glycemic benefit appears to be specifically encouraged.

The complex full document is available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/2008-D-0118-gdl.pdf>.

having 476 sets of measurements over mean follow-up of 10 years, finding mean decline in GFR of 1.7, 0.4, 0.8, 0.7, 0.9, and 1.8 ml/min/1.73 m² per year, respectively. Serial measurement of cystatin C appeared to be more accurate than creatinine-based GFR estimates. Beauvieux et al. (abstract 750) measured isotopic GFR in 124 diabetic persons, confirming that cystatin C gave the most accurate estimate, with CG and MDRD as well as the Mayo Clinic quadratic equation based on serum creatinine being less useful in this regard. Costacou et al. (abstract 223) compared the GFR measured from 24-h creatinine clearance, and by the CG and MDRD formulas, in 426 type 1 diabetic persons followed biennially for 16 years, at which time 14, 12, and 19% had GFR <60 ml/min/1.73 m², of whom 35, 30, and 24% required dialysis or transplantation. Again, the MDRD formula appeared less accurate in assessment of renal function. Brema et al. (abstract 753) found a mean 19 ml/min greater value for the CG than MDRD GFR in 1,304 type 2 diabetic patients, the difference increasing with greater body weight and decreasing with greater age and serum creatinine level. In a study of another potential approach to

assessment of renal function, Marcovecchio et al. (abstract 222) measured symmetric dimethylarginine and creatinine levels in 417 type 1 diabetic children, with inulin clearance GFR assessment in a subset, finding stronger correlation of GFR with symmetric dimethylarginine than with creatinine, suggesting this to be another approach with the potential to allow more accurate assessment of changes in renal function at early stages of diabetic nephropathy.

James Sowers (Columbia, MI) reviewed further aspects of the association of diabetes with renal disease, emphasizing that CKD and albuminuria are associated with increased rates of cardiovascular disease (CVD) and mortality (3), and should be considered parts of the constellation of cardiovascular risk factors in persons with diabetes. “There is a relationship,” Sowers said, “between vascular disease and kidney disease,” even beginning at levels of albuminuria below those customarily thought to be abnormal. He illustrated the importance of what might be termed “premicroalbuminuria” and of reductions in GFR, showing that both are associated with increased risk of CVD. Renal disease, like

diabetes, impaired glucose tolerance, and even having a family history of diabetes (4), is associated with abnormalities of vasodilation mediated by endothelial derived nitric oxide (NO), suggesting linkage between vascular and metabolic abnormalities. Excess generation of reactive oxygen species occurs in both the vasculature and the kidney. Angiotensin II and aldosterone, interacting with pulse pressure and increased systolic blood pressure, activate NADP oxidase as what appears to be a common mediator of oxidative stress. Angiotensin II increases NO metabolism to peroxynitrite (5). The hemodynamic stress of systolic hypertension with loss of vascular compliance further impairs endothelial-derived vasodilation.

Another common denominator is the association of both diabetes (6) and renal disease (7), as well as hypertension, smoking, hyperlipidemia, and normal aging, with a decrease in the ability to produce endothelial progenitor cells (EPCs), which can be quantitated with the cellular marker CD 34, leading to increased CVD risk. These cells derive from bone marrow, play a role in replacing damaged endothelium, and are reduced in people with decreased endothelium-dependent vasodilation (8). Both angiotensin II and aldosterone inhibit production of EPCs, while ARBs (9) and ACEIs increase their levels. Sowers suggested that the direct renin inhibitor aletrisin has similar benefits in renal disease to those of ARBs. Non-hemodynamic effects of inhibition of the renin-angiotensin-aldosterone system also include anti-inflammatory actions. Statins, colony stimulating factor, and lifestyle factors such as physical exercise also appear beneficial.

Dyslipidemia can promote kidney disease, while there are a number of studies suggesting that statins retard CKD progression (10,11), with Sowers citing recent studies suggesting that the combination of statins with ACEIs or ARBs have particular benefit in reducing proteinuria. Sowers discussed the relationship between dyslipidemia and CKD, with the hypothesized mechanism of statins being an increase in endothelial NO synthase transcription and stability, in part via the phosphatidylinositol 3-kinase (PI3K) pathway, via statin-induced inhibition of the mobilization of small molecular weight G-proteins. In a mouse model overexpressing renin, hypertension and insulin resistance are seen, albuminuria increases, and there is oxidative stress associated with increased NADPH oxidase

activity, with improvement in these parameters as well as in renal histology following treatment with an ARB or a statin.

Anemia is also associated with decreased EPCs, with the link appearing to be reductions in erythropoietin levels. EPCs are present in the heart and in the kidney, and treatment with erythropoietin increases EPCs (12). Aung et al. (abstract 767) studied 765 diabetic inpatients, finding that 6% of those with GFR >60 ml/min per 1.73 m², 27% of those with GFR 30–60 ml/min per 1.73 m², 44% of those with GFR 15–30 ml/min per 1.73 m², and 77% of those with GFR <15 ml/min per 1.73 m² had hemoglobin <11 g/dl, with 0, 30, 61, and 65%, respectively, receiving an erythropoiesis stimulating agent, suggesting the need to screen for anemia and offer appropriate treatment in all diabetic persons with GFR <60 ml/min per 1.73 m². When asked about clinical evidence of a benefit of erythropoietin, Sowers noted that doses raising hemoglobin excessively may have adverse effects, suggesting it is preferable to “use a number of [treatments] together.”

Keith Norris (Los Angeles, CA) discussed differences by race/ethnicity in nephropathy progression. Despite similar relative prevalences of early stages (1–3) of CKD among persons with diabetes from different ethnic groups, there is a higher prevalence of ESRD in certain groups, suggesting that factors contributing to initiation may not mediate progression (13). For example, although the rate of growth in ESRD due to diabetes and to hypertension has leveled off over the past 4 years, this is not the case among young African Americans. In the U.S., annual ESRD costs are approximately \$35 billion, with the greater incidence of ESRD among racial minorities adding more than \$10 billion to this figure, pointing to its importance. There are racial differences in blood pressure (14,15). Much of the effect of ethnicity, though, appears more related to disease risk factors and socio-cultural factors than to inherent differences. Studies in Australian minorities show that marginalization from the majority society, discrimination, and loss of traditional culture all have contributed to the stresses leading to greater prevalence of disease. In the U.S., 12% of Caucasians but 35% of Hispanics and 20% of African Americans lack health insurance, another important factor. In a Los Angeles workforce literacy project in 2004, 48% of adults were functionally illiterate, unable

to read a bus schedule or fill out a job application, with even greater prevalence of illiteracy among non-English speakers.

Norris discussed a meta-analysis of 11 studies comprising 1,860 nondiabetic participants with mean proteinuria of 1.8 g daily, 6% of whom were African Americans, in which ACEI decreased the rates of doubling of proteinuria and of progression to dialysis only in persons with >500 mg/day proteinuria. A study of persons with nondiabetic nephropathy comparing maximal doses of the ACEI trandolapril, the ARB losartan, and the combination of the two, however, suggested decreased progression to doubling of creatinine or ESRD in all strata of proteinuria, with a 42% reduction in progression to doubling of creatinine or renal failure for every 10% reduction in proteinuria (16). In the African American Study of Kidney Disease of more than 1,000 persons treated with amlodipine, ramipril, or metoprolol, ramipril led to the greatest reduction in events, with baseline GFR, proteinuria, and the 6-month change in proteinuria important predictors of the risk of developing ESRD (17). In the Reduction in Endpoints in Noninsulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, the change from baseline in albuminuria stratified by ethnicity showed no effect of race, while >1.5 g albuminuria/g creatinine was associated with increased risk of ESRD (18,19). Individuals with the greatest degree of albuminuria reduction had the greatest reduction in ESRD risk, although this protective effect was less pronounced among African Americans. Norris concluded that changes in proteinuria are predictive of diabetic nephropathy progression and that there is no evidence of significant differences in this response across race/ethnicity, suggesting benefit of treatment addressing proteinuria.

Charles Heilig (Chicago, IL) discussed renal glucose transporter expression and its relationship to the development of diabetic nephropathy (20). All of the glucose transporters, GLUT1–6 and sodium glucose transporter (SGLT), are expressed in renal glomeruli and tubules, with GLUT1 the major mesangial glucose transporter. GLUT 1, with 12 transmembrane-spanning helices acting to transport glucose across the plasma membrane along the concentration gradient, is regulated by glucose; its expression regulates extracellular matrix production, acting as a facilitated transporter. Glomer-

ular GLUT1 increases early in a diabetic mouse model in which glomerulosclerosis and albuminuria develop. Mesangial cell GLUT1 levels are increased by high glucose levels, and also by insulin-like growth factor-1, protein kinase C (PKC), transforming growth factor (TGF) β 1, and vascular endothelial growth factor (VEGF), as well as by mechanical stretching. GLUT1, in turn, by increasing intracellular glucose, increases activator protein-1 (AP-1), a transcription factor increasing matrix production, as well as having positive feedback in increasing TGF- β 1 and PKC. GLUT1 increases both the expression and activity of aldose reductase, leading to accumulation of sorbitol; increases glycolysis and lactic acid production; and increases extracellular matrix production, even in the absence of diabetes. Mesangial cells overexpressing GLUT1 show increased production of both types I and IV collagen, as well as increased fibronectin and laminin production, leading to a phenotype similar to that of diabetes. In contrast, antisense inhibition of GLUT1 in cultured mesangial cells suppresses GLUT1 mRNA and protein, decreases glucose uptake, and in vitro appears to protect cells from the effects of high glucose exposure. In animal models, GLUT1 overexpression in glomeruli creates a nephropathy phenotype resembling that of diabetic renal disease with increased mean glomerular volume, mesangial expansion, and sclerosis. Glomerular PKC- β 1 involved in matrix production, vascular endothelial growth factor (VEGF), type IV collagen, and fibronectin levels increase, and over time the animals develop increasing levels of albuminuria and plasma creatinine. In an antisense GLUT1 in vivo study with *db/db* mice, decreased GLUT1 expression reduced glucose uptake and decreased progression of glomerulosclerosis, with protection against matrix accumulation and partial suppression of albuminuria development. In many animal models with hypertension associated with increased glomerular GLUT1, only animals with intra-glomerular hypertension manifest the phenomenon, suggesting it to be mediated by a mechanical stretch of mesangial cells. Subjecting this tissue to stretching in vitro increased GLUT1 expression, a phenomenon inhibited by anti-TGF- β 1 antibody (21). Glomeruli of the Milan hypertensive rat show increased GLUT1 expression, which is further increased by diabetes (22). It appears that connection of the mesangium with

glomerular basement membrane involves contractile filaments. Glomerular capillary changes in volume or pressure increase stretch of mesangial tissues. Early development of renal failure in murine models is associated with particular increase in mesangial GLUT1 expression. Strains developing glomerulosclerosis also have increased VEGF levels, and albuminuria is associated with activation of PKC- β 1, further suggesting that all the components of GLUT1 regulation correlate with renal disease.

Helig reviewed the developing literature suggesting that human diabetic nephropathy is associated with certain susceptibility alleles of GLUT1 (13). Both persons with type 1 and type 2 diabetes have been studied, with certain single nucleotide polymorphisms appearing to convey particular risk; the combination of certain aldose reductase and GLUT1 alleles appear to be particularly associated with risk. Meta-analyses have not fully confirmed the association of GLUT1 polymorphisms with renal disease risk (23), but current studies examining a novel polymorphism showing strong association with the TT-2841 genotype appear to show further evidence of an association (24). Helig noted that in an overexpression model, there was a 10-fold increase in GLUT1, associated with a five-fold increase in glucose uptake, but with increased glucose metabolism rather than increased intracellular glucose levels. Furthermore, while IGF-1 increases GLUT1, insulin has little effect, suggesting a complex regulation of the process.

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