J Am Soc Nephrol 14: 1355–1357, 2003

Overview: Combating Diabetic Nephropathy

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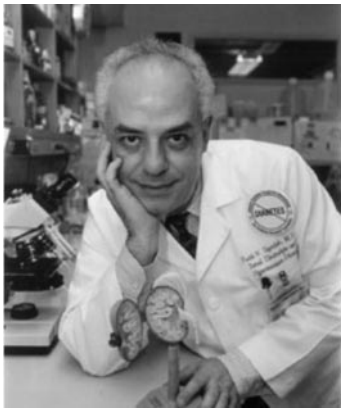

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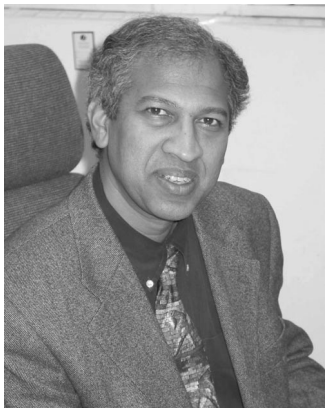

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Much has been said in the scientific and lay media about the growing epidemic of diabetes around the globe, but individuals and societies should never lose sight of the immeasurable human suffering and the enormous healthcare costs that this epidemic exacts. With the growing population of type 2 diabetes, the prevalence of diabetic nephropathy is on the rise, and there is an urgent need to define the pathophysiologic mechanisms for this devastating disorder. Genetic factors conspire with metabolic and hemodynamic insults to induce renal injury in susceptible individuals. In the current issue of the *Journal of the American Society of Nephrology*, four authoritative papers provide a balanced overview of the pathogenesis of the disease along with a comprehensive update on the clinical aspects and current management of diabetic nephropathy. Only by translating the new understanding of diabetic nephropathy into medical practice and implementing widespread clinical guidelines will we ever ensure that all at-risk patients receive the ideal care to stem the epidemic and stop nephropathy in its tracks.

The underlying basis of diabetic complications is the result of prevailing levels of hyperglycemia. This metabolic view became universally accepted only a decade ago thanks to the definitive results of landmark clinical trials, namely The Diabetes Control and Complications Trial in type 1 diabetes and the UK Prospective Diabetes Study in type 2 diabetes. A key step linking glucotoxicity to cell dysfunction in diabetic nephropathy is the excess accumulation of extracellular matrix (ECM) within the glomerulus and the interstitium (1,2). The dominant role of the profibrotic cytokine Transforming Growth Factor-β (TGF-β) has received much support as a critical mediator of the glucotoxicity-induced accumulation of mesangial matrix (3). The many metabolic and humoral factors that are characteristic of the diabetic milieu all converge on a downstream pathway to stimulate the expression of TGF-β and its signaling receptors in the kidney (4,5). TGF-β also links the metabolic theory with the hemodynamic theory, as intraglomerular hypertension is a potent stimulus for activating the renal TGF-β system (6). In fact, TGF-β successfully fulfills all of Koch's postulates, which qualify it as a causative agent of mesangial ECM expansion and renal insufficiency in diabetic nephropathy (7,8). Studies in experimental models have been extended into the human condition (9,10), and the renal TGF-β system is now the focus of several interventional strategies. The review by Mason and Abdel-Wahab elegantly compiles the available data on ECM metabolism in kidney cells and the roles of TGF-β and a relative newcomer, Connective Tissue Growth Factor (CTGF). The fibrotic actions of CTGF are largely driven by TGF-β, but there are also TGF-β-independent effects. The authors further expand on Brownlee's recent unifying postulate (11) that oxidative stress, driven by glucose metabolism and glycated proteins, provides the initial or upstream trigger for activating a multitude of seemingly disparate steps involved in the microvascular complications of diabetes.

The cellular basis of glucotoxicity is reviewed by Haneda and colleagues. The review focuses on key steps involved in glucose uptake into glomerular mesangial cells and the consequent stress induced by glucose metabolism. One important consequence of glucose-stimulated TGF-β is the upregulation of the insulin-independent Glut-1 transporter in mesangial cells (12). Increased glucose entry also leads to stimulation of the protein kinase C (PKC) pathway, and several reports have identified the activation of one or more PKC isoforms. Moreover, the role of members of the mitogen-activated protein kinase (MAPK) pathway has received recent recognition as an additional signaling step involved in mediating ECM produc-

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1046-6673/1405-1355
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000065608.37756.58

tion. Clinical trials are underway with a selective PKC-beta inhibitor (13) to address the role of this kinase isoform in relation to diabetic retinopathy and nephropathy.

Cellular dysfunction due to hyperglycemia may also involve non-enzymatic pathways. Accelerated non-enzymatic reactions involving glucose-protein adducts in diabetes, resulting in Amadori-modified proteins (14,15) and the later-developing advanced glycation end-products (AGE) (16), bring about not only a direct chemical modification of circulating or tissue proteins but also induce oxidative stress and can trigger cellular signaling and activate gene expression through specific receptors. The review by Schmidt *et al.* expands on the exciting biology of RAGE (Receptor for AGE), the most studied member of the AGE-receptor family over the past decade and a potentially important target of therapy. They report that blockade of RAGE in diabetic mice prevents the overexpression of TGF-β and ameliorates the glomerulopathy of diabetes. Because RAGE expression in the glomerulus is principally localized to the podocyte, this receptor system may play a more encompassing role in the development of proteinuria and glomerulosclerosis, whether caused by diabetes or other diseases.

While we wait for clinical translation of these basic science advances to arrest or reverse the course of diabetic nephropathy, Ritz and Wolf challenge the renal and endocrine communities to persevere in implementing the established guidelines for patient management. An approach designed to ensure that glycemia levels are controlled, that the lowest tolerable BP is attained, and that cardiovascular risk factors are likewise seriously addressed holds the greatest promise in providing the largest benefits to the patient. This is a critical viewpoint that needs to be embraced by practitioners and patients alike. But, alas! Only a trivial minority of patients in most practices actually meets the optimal goals of therapy for long periods of time.

Future challenges in diabetic nephropathy are multiple and daunting: widely implement practice guidelines, prevent cardiovascular complications, design new therapies to combat renal fibrosis, decipher the genetic basis of diabetes and its complications, cure type 1 diabetes, prevent obesity, and reduce the incidence of type 2 diabetes. Thus a pessimist's view has emerged among some practitioners despite the significant, but arguably modest, achievements in slowing the progression of kidney disease with glycemic control and BP management. But the long war on diabetic nephropathy is winnable with a coordinated attack on multiple fronts. There is much optimism in the air if we implement a multi-pronged approach. Success stories have recently come from different directions, *e.g.*, the increased public awareness that inevitably has helped to secure increased funding for basic and clinical research by the private and public sectors, the development of consensus guidelines for clinical practice by major medical organizations, the newfound interest on the part of major pharmaceutical companies to develop novel antifibrotic strategies, the recent formation by the National Institutes of Health of a consortium to develop better mouse models of diabetic nephropathy, and many other examples. With renewed hope of novel therapies, the future looks bright. Clinicians and patients alike eagerly look forward to the day when chronic dialysis can be indefinitely postponed! Meanwhile, common sense tells us that strict adherence to tried-and-true disease prevention approaches can effectively and almost immediately reduce the burden of diabetic nephropathy while we wait for innovative cures. Slow and steady wins the race.

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