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EDITORIAL

Risk factors in diabetic nephropathy

R. V. Jayakumar

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Diabetes morbidity and mortality is mainly determined by the late chronic complications of diabetes. Though the macrovascular complications affecting the heart is the leading cause of mortality in diabetes, nephropathy is slowly becoming an important factor in determining the final outcome. This is because of better prevention and treatment of cardiovascular problems with the availability of newer drugs and devices, thereby making diabetic patients live longer. Also it is a well accepted fact, that patients of diabetic nephropathy are more predisposed to cardiovascular and peripheral vascular diseases. Even though the hyperglycemia is closely related to the development of microvascular complications, the evidence of direct relationship between hyperglycemia and nephropathy is less convincing in humans, as only 30% of diabetic patients develop clinical nephropathy [1]. Majority of patients escape renal failure even though some histological evidence of renal damage is present in many. It is unclear why some diabetic patients are more susceptible than others for the development of renal disease. Inherited factors may be providing protection from susceptibility to diabetic nephropathy, but evidence is lacking as to which factors are important. Familial predisposition to raised arterial pressure increases the susceptibility to renal disease in patients with diabetes. Studies have demonstrated that mean blood pressure levels are significantly higher in those who progress to microalbuminuria, than in those who do not, indicating that hypertension is an important risk factor for diabetic nephropathy [2]. There is evidence of familial clustering of diabetic nephropathy in type 2 diabetes and the affected sib-pair linkage analysis have identified loci associated with diabetic nephropathy in type 2 diabetes [3, 4]. Interstingly, in Pima Indians blood pressure levels before the onset of diabetes, predicts the future risk of developing nephropathy [5]

Factors determining the occurence and progression of diabetic nephropathy include hyperglycemia, hypertension, hyperlipidemia and genetic factors. From a clinical patient management point of view, reversible or treatable factors like hypertension, hyperlipidemia and hyperglycemia are important. At present genetic factors may be important only for theoretical discussion, but with the rapidly advancing field of gene therapy, it may be possible to modify the risk factors for diabetic nephropathy favourably by gene therapy.

Genes involved in the genetic predisposition to diabetic nephropathy, are likely to be those involved in renin-angiotensin system, nitric oxide pathway, aldose reductase pathway, GLUT-1, and lipoproteins metabolism. These have been investigated, but studies have, by and large, been inconclusive or shown only weak associations [6]. However, a strong association between polymorphism in the 5′ end of aldose reductase gene and the development of diabetic nephropathy in type 1 diabetes has been confirmed by many investigators [7].

Renoprotective effects of good glycemic control has been demonstrated in many longitudinal and intervention studies, the most famous being DCCT and UKPDS studies. Also reversal of already established structural changes in the kidney has been achieved by maintaining near-normal glycemia by pancreatic transplantation in a small number of type-1 diabetic patients [8]. Hyperglycemia increases the risk of progression of diabetic nephropathy predominantly by altering the functioning of anti-oxidant system. It accelerates the chemical modification of the proteins and

R. V. Jayakumar (✉)
Amritha Institute of Medical Sciences,
Kochi, India
e-mail: rvjayakumar@aims.amrita.edu

lipids leading to the increased formation of Advanced Glycation End products (AGE), Advanced Oxidized Lipid End Products(ALE) and Advanced Oxidation Protein Products (AOPP).

The AGEs have been shown to produce renal damage in both humans and experimental diabetes. AGEs directly alter the structural and functional properties of extra-cellular matrix proteins, increase their rigidity, and favour the trapping of LDL and immunoglobulin-G. The interaction of AGEs with its receptors in the kidney induces the synthesis and release of many cytokines like TGF-b1, and IGF and results in enhanced production of collagen, laminin and fibronectin. Also there is over expression of receptors of AGE (RAGE) in glomerulus and tubular epithelial cells and the AGE-RAGE complexes can produce tubulointerstitial fibrosis[9].In this issue of the journal, Sandeesh Mohan et al. has shown that increased pool of AGEs, ALEs and lipid peroxidases in diabetics, increase proteinuria in all stages of diabetic nephropathy [10].

AGE-RAGE interaction promotes polymorphonuclear leukocyte generated cascade of highly reactive oxygen species, which ultimately lead to production of lipid peroxidases and AOPP. Lipid peroxidation products like ALEs and lipid hydroxyperoxidase produce endothelial and glomerular basement membrane injury by altering proteins like nephrin and connectin and thereby resulting in proteinuria. Lipo-oxidation and gluco-oxidation products have been co-localized in renal tissues of diabetic patients indicating co-existance of glucotoxicity and lipotoxicity.

Hyperglycemia induced activation of polyol pathway leading to kidney damage has been postulated in the pathogenesis of diabetic nephropathy. In animal studies there has been evidence that aldose reductase inhibitors have reduced the albumin excretion rates, but no convincing effect of aldose reductase inhibitors has been shown in controlled studies in humans. So far it appears that activation of polyol pathway may be more likely to be epiphenomena in the setting of diabetic nephropathy, rather than the main factor in the pathogenesis.

High glucose concentration in experimental studies, involving isolated glomeruli, have shown alteration of extracellular matrix formation. High concentration of glucose in mesangial cells cause hypertrophy, increase gene expression and protein secretions like collagen, laminin and fibronectin. [11]. Hyperglycemia also reduces the activity of metalloproteases, enzymes responsible for extracellular matrix degradation.

One of the important predictors of decline in renal function in diabetic nephropathy is the amount of proteinuria. Increasing quantity of proteinuria is a risk factor, indicating progressive renal damage in diabetic nephropathy. Similarily urinary excretion of immunoglobulins, which are large molecules, will help to predict the severity of nephropathy. In this issue of the journal, Sandesh Mohan et al. has shown that urinary immunoglobulin-G/creatinine ratio has a significant association with eGFR and increased odds for potential hazardous factors. Excessive protein overload, leads to excessive protein reabsorption and consequent accumulation of protein in the tubular epithelial cells and these induce the release of vasoactive and inflammatory cytokines. These cytokines lead to local injury, infiltration of mononuclear cells and ultimately renal scarring and insufficiency. The tubular toxicity of protein raises the possibility that the beneficial effect of ACE inhibitors is also through its anti-proteinuric effect other than its hemodynamic effects.

Numerous studies looking at the cellular and molecular mechanism of renal damage in diabetic nephropathy, lead to the unifying concept that the insults of hyperglycemia, hypertension and proteinuria converge at the cellular level by using similar molecular signaling pathways and influencing the expression of common cytokines. The important cytokines that are implicated in the diabetic nephropathy are Transforming Growth Factor b1(TGF-b1),Connective tissue growth factor (CTGF), Insulin like growth factor (IGF), Vascular Endothelial Growth Factor (VEGF) and Angiotensin-2. All these cytokines induce tissue injury, thicken the basement membrane and alter the permeability producing proteinuria and scarring.

During the last couple of decades, a number of advances have been made in understanding the pathogenetic mechanisms and risk factors for the development of diabetic retinopathy. In a recent study from India, the risk factors determining the diabetic nephropathy in urban Asians are the duration of diabetes, the diabetic control and systolic blood pressure [12]. The consensus is that hyperglycemia by its action through glucotoxicity and lipotoxicity, hypertension and proteinuria contributes to nephrotoxicity in diabetics. All these factors induce oxidative stress which trigger the release of various tissue damaging cytokines which produce the renal damage. The amount of proteinuria and the renal loss of immunoglobulin-G may help to assess the risk in diabetic retinopathy. From the treatment point, tight control of blood glucose, blood pressure, and using drugs affecting renin-angiotensin system, cytokine production and anti-oxidants, may all help to salvage the renal damage. Finally, the prevention or slowing the progression of diabetic nephropathy will significantly improve both the patient's quality of life and reduce the public health expenditure.

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