EDITORIAL

Diabetic Nephropathy: Disease Burden, Pathophysiology and Therapeutic Approaches

Diabetic nephropathy (DN) may be defined clinically by the presence of elevated urinary albumin excretion, or impaired renal function or both in patients with diabetes mellitus (DM) and diabetic retinopathy (DR). It is estimated to develop in 25% to 40% of patients with type 1 DM (T1DM) and 5% to 40% of patients with type 2 DM (T2DM) and is the major cause of end-stage renal disease (ESRD) worldwide. Over 20% of patients with T2DM may be detected to have DN at the time of DM diagnosis and a further 20% to 40% develop DN within the next 10 years.[1]

A progressive decline in glomerular filtration rate (GFR) in the absence of albuminuria in T2DM has been observed in several landmark studies including NEPHRON, UKPDS and ADVANCE. Hence, such non-albuminuric renal impairment in T2DM has been termed as non-classical DN that is not observed to be associated with poor metabolic control, retinopathy or hypertension but is linked to a higher cardiovascular risk and is thought to be a consequence of macroangiopathy.[2]

DN is classically described as a glomerulopathy associated with diffuse or nodular glomerulosclerosis, electron microscopic studies have revealed tubulointerstitial, glomerulosclerotic and vascular changes of varying proportions, as such, ultimately one-third will present with classical DN, one-third with non-diabetic kidney disease (mostly obesity-related focal segmental glomerulosclerosis in the absence of retinopathy) and one-third with mixed pathologies.[3]

Endothelial dysfunction plays a central role in the pathogenesis. Excess angiotensin-2 and TGFâ1 stimulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase leading to excess reactive oxygen species accumulation and thus activation of different intracellular metabolic pathways including the polyol and hexosamine pathway, increased production of advanced glycation end-products (AGEs), activation of protein kinase C (PKC) and p38 mitogen activated protein kinase (MAPK) ultimately causing glomerular hypertension and tubulointerstitial fibrosis. In addition, there is podocyte effacement, mesangial expansion, and mesangiolysis causing glomerular filtration barrier disruption leading to proteinuria.[4]

A number of novel diagnostic and prognostic biomarkers including cystatin C, copeptin, endostatin, neutrophil gelatinase-associated lipocalin (NGAL), beta-trace protein (beta TP) and microRNA-130b (miR-130b) have been explored.[5]

Lifestyle modification, good metabolic control along with renin-angiotensin-aldosterone system (RAAS) blockade [angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)] have been the key therapeutic approach for combating DN. The use of aldosterone antagonist as an add on therapy has demonstrated a reduction in albuminuria and renal disease progression.[6] Recent studies have confirmed the cardio-renal protective benefits of the sodium-glucose co-transporter-2 (SGLT2).[7,8] The anti-inflammatory and reno-protective properties of glucagon-like peptide 1 (GLP-1) analogues through the incretin pathway has been recently proposed with promising results.[9,10]

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