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GUEST EDITORIAL

Diabetic nephropathy: associated risk factors in renal deterioration

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Diabetic Nephropathy (DN) is now recognised as the leading cause of end stage renal disease (ESRD) and contributes between 20 and 40 % of patients with chronic kidney disease on renal replacement therapy (dialysis), worldwide [1]. Clinically, microalbuminuria is considered as the earliest sign of evolving DN, which may become persistent and progressive, leading to proteinuria due to combination of several factors such as chronic hyperglycemia, uncontrolled hypertension, ethnicity, family history of renal disease, lack of early intervention and/or suboptimal glycemic control [2].

Established DN is defined as presence of persistent proteinuria of >0.5 gm/day, hypertension and a progressive decline in the glomerular filtration rate (GFR), leading to ESRD [3]. Traditionally, the initiation and progression of diabetic nephropathy has been described to go through five different stages such as glomerular hyperfiltration, incipient nephropathy, microalbuminuria, overt proteinuria and end-stage renal disease [4]. In the Indian diabetes population, the prevalence of persistent microalbuminuria and DN has been reported to be approximately 27 and 2.2 %, respectively [5].

In subjects with type 1 diabetes, proteinuria has been reported to manifest in about 15–40 % of patients, and is generally seen in those with history of about 15–20 years of diabetes duration [6]. The prevalence of proteinuria in subjects with type 2 diabetes is highly variable with reported incidence ranging between 5 and 20 % in different populations [7]. The onset of proteinuria is associated with a significantly progressive decline in the GFR, with an average drop of approximately 10–12 ml/min/year [8]. There is a significant inter-individual difference in the rate of deterioration in type 1 and type 2 diabetes, however, the collective risk of progression to ESRD after 5 years of persistent proteinuria is approximately 60 % in both type 1 and type 2 diabetes [9].

In view of the increasing number of diabetes subjects progressing to ESRD, it is vital to identify the risk factors for deterioration of renal function to develop appropriate intervention therapies, to arrest the progression of DN. Perhaps, due to different etiopathogenesis, type 1 and type 2 diabetes subjects with nephropathy have been reported to have differential inter-individual rate of decline in renal function, as reflected by GFR [3, 10]. Although, progressive proteinuria is known to be the single most important factor for decline of renal function in DN, there are several other associated risk factors, which may significantly increase the risk of renal deterioration.

In type 1 diabetes subjects, several risk factors such as high normal urinary albumin excretion rate, male gender, hypertension, glycemic control (HbA1c), small height at baseline contribute to the evolution of persistent microalbuminuria [6]. In type 1 diabetes subjects with established DN, hypertension, albuminuria, hyperglycemia and hypercholesterolemia have been reported to promote the deterioration of renal function [3].

In type 2 diabetes subjects, baseline level of albuminuria, systolic blood pressure, glycemic control (HbA1c), GFR, age, heavy smoking, anemia and grade of retinopathy (none/background, proliferative), have been reported to be significant predictors for progressive renal failure as determined by rate of loss of GFR and time to doubling of baseline serum creatinine [11]. Surprisingly, gender, diabetes duration, diastolic blood pressure, body mass index and lipid levels did not show any significant association with progressive loss of GFR in this study [11].

Although baseline albuminuria and GFR are significant predictors of progressive renal deterioration, baseline albuminuria has been reported to have greater odds ratio for

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deterioration of renal function, as compared to baseline GFR [12]. About 40–55 % of type 2 diabetes subjects have been reported to have reduced GFR in absence of microalbuminuria/proteinuria [13, 14]. This may be due to complex etiopathogenesis of type 2 diabetes and is also reflected in the histological presentation with only 30 % having classical findings of thickening of glomerular basement membrane and mesangial expansion, the other 30 % with normal renal structure and the remaining 40 % having predominant tubulointerstitial lesions such as tubular atrophy and tubular basement membrane thickening with relatively mild glomerular changes [15].

In a subset analysis of UKPDS study on type 2 diabetes subjects to determine the factors for decline in renal function, a diverse set of predictors were identified for progression of albuminuria and progressive decline in GFR [16], suggesting an interplay of complex mechanisms in the manifestation of both these pathological processes. Persistent microalbuminuria has been considered to be the most important risk factor for development of proteinuria, however, not all patients with microalbuminuria progress to overt proteinuria neither do all patients with deteriorating GFR have preceding microalbuminuria/proteinuria [16], which is intriguing.

Clinically, presence of persistent microalbuminuria in diabetes subjects warrants intervention therapies to prevent its progression. With the introduction of angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) group of anti-hypertensives, the rate of progression from microalbuminuria to proteinuria in type 1 diabetes subjects has seen a significant drop from as high as approximately 80 % [17] in the eighties to 44 % in the last decade [18]. However, a significant number of diabetes subjects continue to have progressive disease in spite of the above therapies, suggesting presence of other factors such as oxidative stress and/or genetic predisposition. Unfortunately, the above mentioned studies [3, 6, 11, 16] on progression of DN in type 1 and type 2 diabetes subjects were not designed to examine the contribution of oxidative stress or any genetic factors.

Ongoing oxidative stress in the glomerulus and tubules, as a result of chronic hyperglycemia has been proposed to be a major culprit in the initiation and progression of diabetic renal disease [19] and containment of oxidative stress has been shown to delay the progressive decline in GFR [20]. Chronic hyperglycemia promotes oxidative stress injury directly through processes such as enhanced production of advanced glycation end products (AGEs), enhanced reactive oxygen species (radical molecules such as superoxide, hydroxyl, peroxyl and non–radical molecules such as hydrogen peroxide and hydrochlorous acid) generation, reduced production of antioxidants such as nitric oxide, increased cytokine activity, enhanced inflammatory markers and endothelial dysfunction [1]. In addition, chronic hyperglycemia modulates several metabolic pathways such as oxidative phosphorylation, sorbitol/aldose reductase pathway or the polyol pathway, mitochondrial electron transport chain (ETC) and NAD(P)H oxidase [21] leading to enhanced oxidative stress burden with increased ROS formation and reduced NO production.

In conjunction with chronic hyperglycemia, oxidative stress may orchestrate several functional and structural abnormalities in the glomerulus and tubulointerstitium such as enhanced deposition of extracellular matrix in the mesangium, promotion of a hypoxic environment in the tubulointerstitium, enhanced oxidant injury and tubular apoptosis leading to tubulointerstitial fibrosis even before the onset of microalbuminuria [22], a state of generalised endothelial dysfunction [6], which may further aggravate the condition. Ongoing cellular oxidative stress has been postulated to be a significant factor in the progression of renal diseases [20]. With chronic hyperglycemia as a permanent feature, it is plausible that irrespective of microalbuminuria/proteinuria, oxidative stress plays a vital role in the progression of DN and contributes to renal deterioration [23].

Although it seems an exciting proposition, the confirmatory/contributory role of oxidative stress in the pathogenesis and progression of DN is yet to be established. Normally surrogate markers of oxidative stress, such as measurement of capacity of the vascular endothelial cells to release nitric oxide in response to ischemic stimuli is tested to determine the anti-oxidant response [24]. This is primarily due to lack of standardised tools to measure and quantify oxidative stress in chronic diseases including DN. The measurement of ROS in serum is hampered due to highly reactive nature of these molecules. Research studies in estimation of oxidative stress currently measure the total antioxidant buffering capacity of plasma or specific markers of free radical-mediated damage such as F(2)-isoprostane or oxidised-LDL (Ox-LDL) [25]. However, the robustness and consistency of these methods are yet to be validated in big populations and they largely remain research tools at the moment — far away from their application in a clinical setting.

In conclusion, the initiation and progression of DN is a complex process with varied contribution of several diverse metabolic and pathogenic processes in the background of chronic hyperglycemia. Baseline hypertension, albuminuria, glycemic control and dyslipidemia are common determinants of progressive decline in renal function in both type 1 and type 2 diabetes subjects with established DN, whereas, low GFR at baseline, increasing, age, heavy smoking, anemia and grade of retinopathy are additional factors associated with progressive decline in renal function in type 2 diabetes subjects. In addition, to the above mentioned

contributing factors, ongoing oxidative stress is associated with progressive renal disease [20].

A sizable portion of diabetes subjects do not develop microalbuminuria in spite of chronic hyperglycemia suggesting presence of certain yet unidentified protective factors (genetic or others). In addition, a progressive decline in GFR is also seen in a significant proportion of diabetes subjects without microalbuminuria/proteinuria, suggesting that decline in renal function is not dependent on presence of proteinuria. Hence it is desirable that all diabetes subjects should have measurement of GFR at least annually, along with microalbuminuria/proteinuria to monitor the renal function in general and identification of high risk DN patients who may have significantly greater rate of decline in GFR. Oxidative stress as a result of chronic hyperglycemia appears to be a major contributor to progressive decline in GFR in diabetes subjects and currently lot of research is underway to develop reliable tools to measure and monitor oxidative stress in these subjects.

The treatment cost of DN and its potential consequence such as ESRD is expensive and may not be affordable to a vast majority of the burgeoning population of patients with diabetes in the developing countries. Until specific therapies aimed at arresting progression of renal decline are available, optimum management of hyperglycemia, hypertension, dyslipidemia, lifestyle modification (cessation of smoking, regular exercise, stress free life and balanced diet) and regular monitoring of renal parameters (serum creatinine, albuminuria and GFR) with timely intervention, if required, remains the cornerstone of management of DN in diabetes subjects.

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