Editorial

The Kidney as a Familiar Victim of Diabetes: What we Should Do?

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Editorial

Diabetes Mellitus (DM) is one of the major problems in health systems. This is a serious disease, which may worsen healthy human tissues and organs. The latest global estimate from the International Diabetes Federation is that in 2015 there were 415 million people with DM and that by 2040 the number will be 642 million [1]. Such overall increase in the number of people with diabetes has had a major devastating impact on the kidneys and development of diabetic nephropathy (or diabetic kidney disease the preferred term by WHO). Moreover, diabetes is the leading cause of end-stage renal disease, accounting for approximately 50% of cases in the developed world. With the rising epidemic of DM, obesity and an ageing population, it is anticipated that the burden of renal disease on health systems will increase further [2]. Each kidney contains up to one million filtering units, the nephrons. Diabetes can damage the nephron, leading to development of Diabetic Kidney Disease (DKD). Unfortunately, DKD often has no symptoms or signs until it is well advanced. Therefore, alterations in renal function (albuminuria, reduced glomerular filtration rate) and structure are found even at the onset of DM.

Pathogenesis of DKD is a complex multifarious process that appears to be a jumble of oxidative stress, inflammation, and epigenetic factors. However, the role of glomerular hyperfiltration early in the course of diabetes lies at the heart of pathophysiology of DKD. Pathophysiologic abnormalities in DKD start with long-standing inadequately controlled blood glucose levels. This is followed by numerous changes in the filtration units of the kidneys. At the start, there is dilation of afferent and constriction of the efferent arterioles, resulting in glomerular capillary hypertension and hyperfiltration; this step by step passes to hypo-filtration over time. Alongside, there are morphological changes within the glomerulus itself: a widening of the slit membranes of the podocytes, a thickening of the basement membrane, an increase in the number of mesangial cells, and an increase in mesangial matrix. This matrix invades the glomerular capillaries and produces deposits named "Kimmelstiel-Wilson" nodules.

More and more, the mesangial cells and matrix can progressively expand and consume the entire glomerulus resulting in shutting off the filtration [3,4].

Clinically, an early warning sign of DKD is the emergence of albumin in urine (Albuminuria) with subsequent not desirable general problems with the body's fluid balance resulting in oedema in the legs, feet, face and hands. What is more? albuminuria is associated with local damage to other parts of the kidney, causing microscopic scarring and additional reduced kidney function. That's why, albuminuria is often the first clinical indicator of the existence of DKD and at the same time, it is a clinically useful tool for predicting prognosis and for monitoring response to therapy. However, for several reasons, the sternness of albuminuria does not for all time expect DKD evolution in diabetic. Because of the large number of false positives, tests that provide unusual results should be repeated at least twice over a 3- to 6-month period. Also, albuminuria may be increased by episodic hyperglycemia, high blood pressure, high-protein diet, fever, exercise, congestive heart failure and urinary tract infection. In addition, despite the strength of albuminuria as a risk biomarker for DKD outcomes, there are considerable limitations. Importantly, not all people with DKD and reduced estimated Glomerular Filtration Rate (eGFR) have increased albuminuria. There is no albuminuria in about one third of patients with diabetes who develop kidney disease. The absence of albuminuria in persons with a reduced eGFR and diabetes raises the possibility of nondiabetic chronic kidney disease or associated vascular disease [5]. Alongside albuminuria, DKD is usually linked with a rise in blood pressure and a decline eGFR. However, eGFR does not usually fall until DKD established. But, once the eGFR is reduced, it tends to fall at a steady rate unless the precise management is given.

Are all diabetics prone to kidney problems in similar extent? A number of risks have fingerprint in this regard. Diabetes duration and control, aging and associated hypertension increase the odds that the kidney becomes unambiguous victim of diabetes. About 10% of diabetic patients develop early signs of DKD in the first 10

years and about 20 – 30% by 20 years after diagnosis. Also, a natural slow decline in the eGFR occurs by aging. During adulthood, in the region of 8% of kidney function appears to be vanished with each decade of life. As well, uncontrolled high blood pressure and blood glucose amplify the hazards of more and more kidney damage [6]. One of the repeated question in this area: Is there a link between glomerular hyperfiltration and subsequent albuminuria or a decline in eGFR?. According to Magee et al, a meta-analysis suggested that there was a 2.7-fold increased risk for the advance of microalbuminuria in those with prior hyperfiltration, however this augmented risk was lost when the level of glycemia was taken into account [7]. Studies performed over the last decade now agree to a series of stages in the development of DKD (five stages based on the changes in glomerular filtration rate and urinary albumin excretion). Such a categorization may be useful both in clinical work and in research activities [8,9].

> **Stage 1(pre-nephropathy):** Glomerular hyperfiltration due to hyperglycemia with a subsequent reversible increased urinary albumin excretion (micro-albuminuria), aggravated during physical exercise, eGFR>90 mL/min/1.73 m².

> **Stage 2(incipient nephropathy):** Characterized by morphologic lesions without clinical disease. During good diabetes control, albumin excretion is normal. However, during poor diabetes control albumin excretion goes up both at rest and during exercise, eGFR 60-89.

> **Stage 3(overt nephropathy):** Abnormally elevated urinary albumin excretion (macro-albuminuria) which is higher in patients with increased blood pressure, eGFR 30-59.

> **Stage 4(Kidney failure):** The classic entity characterized by persistent proteinuria (macro-albuminuria >0.5 g/ 24 h). When the associated high blood pressure is left untreated, renal function declines, eGFR 15-29.

> **Stage 5:** Is end-stage renal failure with dialysis, eGFR<15.

Taken as a whole, regrettably, there is no pleasing cure for conventional DKD. Other than, treatments can delay or stop the progression of the disease. At this instant, what we should do to deal with this growing dilemma?: first of all, diabetes prevention must remain at the cornerstone of reducing DKD. Prevention of cardiovascular disease, a major cause of morbidity in DKD, centers upon proper management of obesity, LDL cholesterol and blood pressure. Glycemic control is by logic the nucleus of good diabetes care. However, effects of intensive glycemic control vary with severity of DKD. Those with low eGFR are at high risk for hypoglycemia, an immediate and serious adverse event. The number of oral agents that can be used to treat hyperglycemia in patients with DKD is quite limited due to decreased drug clearance and side effects. Hypoglycemia is often

the main limiting factor in achieving optimal glycemic control and is associated with substantial morbidity and mortality. Moreover, diabetes management is further convoluted by challenges with glycemic monitoring due to a bias to the low of HB A1$_C$ related to discriminating red blood cell turnover [2,10].

Besides dealing with concomitant risk factors, nutritional plan should be modified for advanced DKD (stages 4-5) to reduce hazards of hyperkalemia, hyperphosphatemia, bone mineral metabolism disorders and hypertension. Even small rises in blood pressure need to be treated, as uncontrolled high blood pressure increases the risk of more kidney damage. Pharmacological plan remains a very energetic field with multiple drugs in both human and experimental research channels. There are pros and cons in this summit. Some drugs are promising as a potential precious therapeutic use and some drugs are still under trials [11-14]. For about three decades, renin angiotensin aldosterone system blockade has played an important role in delaying the progression of DKD via anti-hypertensive and anti-proteinuric effects. However, there is emerging data on newer drugs that could mitigate the harmful and deleterious effects of diabetes on renal function. Sodium Glucose Co-Transporter-2 (SGLT-2) inhibitors currently offer more guarantee than most other drugs under active researches. This class of drugs is followed by incretin-related therapies which might confirm optimistic and hopeful role in management of DKD. Though, more researches are needed to hold up their use in reversing, preventing or even delaying the progression of DKD. Furthermore, there is emerging evidence of role of endothelin in the pathogenesis of proteinuria. Consequently, endothelin antagonists are hypothesized to recover albuminuria in addition to causing anti-fibrotic, anti-inflammatory effects. Apart from regulating renal potassium excretion and sodium absorption, mineralocorticoid receptor activation is allied with activation of pro-inflammatory, oxidative, and pro-fibrotic pathways in various organ systems. Therefore, the antagonism of mineralocorticoid receptors may results in anti-inflammatory, antioxidative, and anti-fibrotic effects in DKD. In a similar way, nonspecific phosphodiesterase inhibitor, is known for its antiinflammatory and anti-fibrotic properties in experimental models and might slow the evolution of advanced DKD.

Multiple cohort studies propose that elevated uric acid levels are associated with faster progression of DKD. Therefore, it was hypothesized that lowering serum uric acid levels (by Xanthine oxidase inhibitors) can slow the progression of DKD. Come back to the pathogenesis of diabetic complications, it is known that DM leads to glycosylation and oxidation of proteins, lipids, and various cell surface receptors, leading to the formation of advanced Glycosylation End Products (AGEs) which are now recognized and predicted to be an important pathway through which diabetes contributes to vascular damage. Pyridoxamine

dihydrochloride, a derivative of vitamin B6, is known to inhibit a broad range of mechanisms that are responsible for the formation of AGEs, achievement which could be helpful in dealing with DKD. Adding together, oxidative stress has been proposed as an important mechanism in progression of renal disease. Thus, use of antioxidants could be beneficial. Come to an end and at the moment, a chief imperative question still arises, what is the appropriate commerce in DKD?. Come back to above included different literatures; we may bring to a close answer. Strict blood pressure and glycemic control along with renin angiotensin aldosterone system blockade are tools at our fingertips and still remain the standard of care to delay the progression to end stage renal disease. Inevitably, ongoing serious researches are required to notify the clinicians what has been achieved regarding the use of the other newer mentioned drugs outcomes.

Conclusion

DM is a serious disease has had a major devastating impact on the kidneys and development of DKD or nephropathy. Early pathophysiology of DKD is the glomerular hyperfiltration. Clinically, an early warning sign of DKD is the emergence of albumin in urine. Alongside albuminuria there is a decline in eGFR. However, eGFR does not usually fall until DKD established. But, once it reduced, it tends to fall at a steady rate unless the precise management is given. Renin angiotensin aldosterone system blockade, Sodium Glucose Co-Transporter-2 (SGLT-2) inhibitors, incretins, endothelins antagonist, mineralocorticoid receptor activation, nonspecific phosphodiesterase inhibitor, Xanthine oxidase inhibitors, antioxidants, Pyridoxamine dihydrochloride are promising as a potential precious therapeutic use but most of them are still under trials. Strict blood pressure and glycemic control along with renin angiotensin aldosterone system blockade still remain the reasonable standard of care to delay the progression of DKD to end stage renal disease.

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