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COMMENTARY

From sugar to kidney: A never-ending battle

Diabetes mellitus (DM) has a prominent role in renal impairment, and is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), which place a tremendous burden on the global economy. It is well known that people with DM and CKD have a higher risk of all-cause mortality, cardiovascular mortality, and kidney failure. Diabetic nephropathy (DN) is considered as a micro-angiopathic manifestation of diabetes, but whether DM is a crucial contributor to cardiovascular morbidities and mortality in patients with ESRD remains debatable.

Recently, Schroijen *et al.*[1], the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study group, using data retrieved from the European Renal Association-European Dialysis and Transplant Association Registry between 1998 and 2006, reported that overall mortality was significantly higher in patients with diabetes as primary renal disease (DM PRD) compared with those with diabetes as a comorbid (DM Co-M) condition. The authors reasoned that dialysis patients with DM Co-M have less pronounced multiple system involvement, whereas patients with DM PRD are more likely to have multiple organ damage including retinopathy, neuropathy and cardiovascular complications. In addition, the authors carried out several sensitivity tests to ensure the robustness of their findings. The main strengths of their study are that their results were based on data from national registries of incident dialysis patients diagnosed with DM PRD and DM Co-M. Their findings emphasize some important points for physicians who treat diabetic patients with renal involvement. First, optimal predialysis care should be required in DM PRD patients. Second, dialysis patients with DM PRD should receive early intervention and be closely monitored because of their high mortality rate. Third, healthcare providers and physicians should pay more attention to potential coexisting vascular complications in patients with DM PRD.

However, that study had several limitations, as partly acknowledged by the investigators. First, the lack of standardized assessments across all cohorts was noted; that is, the discrimination between DM PRD and DM Co-M conditions simply relied on the clinical judgments of clinicians and/or histological diagnosis. The accuracy of diagnosis of DN was worrisome and will be discussed later. Second, the differences in the causes of death in each group were not stated. Third, we also wonder if the findings would be different if the statuses of anemia, hyperglycemia and hyperphosphatemia were taken into account, as all three are crucial prognostic factors in ESRD patients. Fourth, medications (for example, frequency of use of erythropoietin injections) used in enrolled patients were not recorded, which might influence the outcomes of these ESRD patients tremendously. Fifth, the data on residual renal function and ethnicity were not provided and hence could not be analyzed. Finally, the possibility of residual confounding from observational data cannot be ruled out.

A previous study by the NECOSAD study group[2], which was a smaller study of Dutch dialysis patients, showed no survival difference between DM PRD patients and DM Co-M patients. The low power of that study was mentioned by the authors. However, both of the NECOSAD studies presented the same problem: the accuracy of diagnosis of DM PRD and DM Co-M. We believe that a lack of a definite diagnosis can lead to variable results. It is worth noting that a meta-analysis carried out by Fox *et al.*[3] emphasized the urine albumin-to-creatinine ratio and the estimated glomerular filtration rate, instead of the presence or absence of diabetes, as the two pivotal predictors of mortality in CKD or ESRD patients, thus implying that kidney disease is still the most significant determinant of final clinical outcome. The authors also point out that cardiovascular complications are critical players, irrespective of whether or not patients have diabetes, hence stressing the importance of controlling risk factors for cardiovascular disease in patients with CKD. Further epidemiological studies using standardized methods for diagnosing and treating DM PRD and DM Co-M patients are definitely required.

Diabetic nephropathy has a broad spectrum of definitions. The exact causes of nephropathy in patients with DM, especially type 2 DM, are relatively diverse and cannot be precisely determined by clinical parameters. As DN is pathologically heterogeneous, the most critical issue is to devise a more precise, but clinically acceptable, definition. In fact, most of the diagnoses of DN in the literature lack renal biopsies. However, one recent study that did include renal biopsy results reported that just 47.8% of type 2 DM patients with overt proteinuria were classified as having DN[4]. In order to achieve higher diagnostic accuracy in DN, reliable biomarkers from urine or blood, or metabolomic studies are currently being investigated. Figure 1 shows the clinical considerations when nephropathy develops in diabetes patients. Although differentiating the contributions of DM PRD and DM Co-M to cardiovascular complications and mortality are not always easy, a recent study using a nationwide cohort in Taiwan followed up from 1998 to 2009 showed that both DM and ESRD synergistically contribute to an increased incidence of cardiovascular events[5].

In conclusion, the awareness of increasing health and socioeconomic problems associated with DN as a global issue reminds us of the need to imple-

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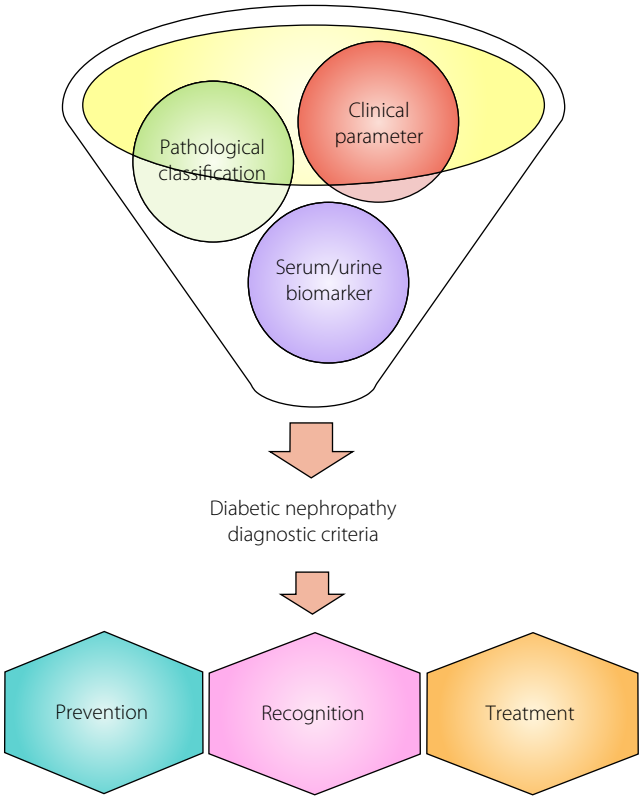

Figure 1 | For development of nephropathy in patients with diabetes, one should consider the clinical features, serum/urine biomarkers and pathological findings, all of which are associated with clinical diagnosis and strategy of management.

ment new strategies involving prevention, recognition, and treatment of DN and its related complications. As patients with DM PRD have a higher mortality rate than those with DM Co-M, accuracy in diagnosis of DN should be emphasized. We anticipate that a convenient staging system or a cocktail of diagnostic criteria including functional parameters (clinical parameters, such as urine albumin-to-creatinine ratio or estimated glomerular filtration rate), anatomical parameters (pathological classifications), and systemic parameters (serum or urine biomarkers) will be created to improve classification and prediction of renal function decline and mortality.

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