Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes

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The incidence and prevalence of diabetes mellitus (DM) continue to grow markedly throughout the world, due primarily to the increase in type 2 DM (T2DM). Although improvements in DM and hypertension management have reduced the proportion of diabetic individuals who develop chronic kidney disease (CKD) and progress to end-stage renal disease (ESRD), the sheer increase in people developing DM will have a major impact on dialysis and transplant needs. This KDIGO conference addressed a number of controversial areas in the management of DM patients with CKD, including aspects of screening for CKD with measurements of albuminuria and estimated glomerular filtration rate (eGFR); defining treatment outcomes; glycemic management in both those developing CKD and those with ESRD; hypertension goals and management, including blockers of the renin–angiotensin–aldosterone system; and lipid management.

Kidney International advance online publication, 30 April 2014; doi:10.1038/ki.2014.128

KEYWORDS: albuminuria; blood pressure; diabetic kidney disease; glycemic control; lipid management

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Received 12 February 2014; revised 19 February 2014; accepted 20 February 2014

The incidence and prevalence of diabetes mellitus (DM) have grown significantly throughout the world, due primarily to the increase in type 2 DM (T2DM), which in turn is largely related to the increase in obesity.[1] This increase in T2DM disproportionately affects less developed countries, which also have fewer resources to deal with such patients.[1] The increase in the number of people developing diabetes will also have a major impact on dialysis and transplant needs. As such, it is important to develop cost-effective strategies at every step: (1) prevention of obesity; (2) screening for and prevention of diabetes in an at-risk population; (3) glycemic control once diabetes develops; (4) blood pressure (BP) control once hypertension develops; (5) screening for diabetic chronic kidney disease (CKD); (6) use of renin–angiotensin–aldosterone system (RAAS) inhibition/blockade in those with diabetic CKD; and (7) control of other cardiovascular (CV) risk factors such as management of low-density lipoprotein cholesterol (LDL-C).

The relationship between CKD and CV disease (CVD) remains complex. Increased urinary albumin excretion rates (AERs) and decreased glomerular filtration rate (GFR) are both associated with an increase in all-cause and CVD mortality independent of each other and of other CVD risk factors in general and high-risk populations.[2–4] The relationship between the presence of microalbuminuria and CVD mortality in diabetic individuals has been known for over 25 years[5] and the interrelationship between AER, GFR, and CVD mortality has been well-studied in diabetic individuals.[6,7] However, treatments that affect progression of CKD may not always have the same effect on the development/progression of CVD. Similarly, there may be differences in how interventions affect urinary AER versus GFR. In patients with diabetes, there appear to be differences in the rate of GFR decline that are related to the presence or absence of increased AER.[7,8]

Studies in both type 1 DM (T1DM) and T2DM have shown that glycemic control can decrease the initial development of

microalbuminuria and macroalbuminuria,[9–12] but data documenting an effect on GFR are sparse.[13–16] Recent data suggest that perhaps there should be different hemoglobin A1c (HbA1c) targets for CKD and CVD, as HbA1c levels below 7% (53 mmol/mol) continue to show benefit in preventing the development of microalbuminuria,[17–19] but show no benefit[17–19] and perhaps harm[20] with respect to CVD. Although there may be only a minimal effect of lower HbA1c levels on CKD as it progresses toward end-stage renal disease (ESRD), other complications of diabetes such as retinopathy and neuropathy may benefit from such control.

Similarly, the blood pressure (BP) targets for CKD and CVD may be different. While it is recognized that BP control is very important in slowing the rate of fall of GFR,[21] the optimal BP to benefit all outcomes is controversial. Similar to the effects of glycemic control, a systolic BP lower than 120 mm Hg may be of further benefit for CKD progression,[22] but could be associated with worsened CVD outcomes.[22–24]

The role of RAAS blockade in the development and progression of diabetic CKD over and above BP control needs re-evaluation. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are not able to prevent the development of microalbuminuria in normotensive individuals with either T1DM or T2DM[25,26] and their role in normotensive individuals with low levels of microalbuminuria is unclear. The relative benefits of ACE-Is versus ARBs versus direct renin inhibitors (DRIs) in T1DM and T2DM patients with hypertension and albuminuria remain to be determined. Similarly, the role of combinations of drugs acting in the RAAS remains controversial. Finally, whether RAAS-blocking drugs have an effect over and above BP reduction in decreasing the rate of CKD progression in those without increased AER is not clear.

Many other controversies exist in the management of diabetic CKD. Although statins likely decrease CVD in those with CKD before needing dialysis,[27,28] the proof that they are effective in patients on dialysis is lacking.[29–31] Should statins be stopped when patients go on dialysis? Are there any efficacy data for other cholesterol-lowering medications in patients with diabetic CKD? Another controversial issue is the use of metformin to control hyperglycemia in patients with decreased GFR. Although lactic acidosis is a potential problem in such patients, the risk appears to be small.[32–34] Whether the current guidelines are too strict deserves a reanalysis.

To address these and other issues, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference on Diabetic Kidney Disease on 16–18th March 2012 in New Delhi, India. Drs Carl Erik Mogensen and Mark E Molitch cochaired this conference with the aim to define the current state of knowledge in the management of diabetic kidney disease (DKD). Topic areas related to DKD included: (1) epidemiology, (2) albuminuria, (3) glycemic control, (4) RAAS blockade, (5) management of hypertension, and (6) role of statins.

Invited participants and speakers consisted of leading worldwide experts on these topic areas, including nephrologists and diabetologists, who gave the broadest views possible on the subject. Their task was to summarize the existing knowledge, develop recommendations on what can be done to optimize the prognosis of patients with DKD based on this knowledge, and to formulate and prioritize research questions. This position statement is the resultant output from the conference.

SCREENING AND EVALUATION OF DKD

The role of albuminuria

Testing for albuminuria—either for screening or for diagnosing—uses the same test for two purposes: to identify people at high risk of subsequent complications (including renal disease, CVD, and death), and to offer treatment. Treatment decisions may depend only on the presence or absence of microalbuminuria (defined either using albumin-to-creatinine ratio or a urinary AER) or on the degree of albuminuria. Microalbuminuria identifies diabetic individuals at higher risk of overt proteinuria and of ESRD[35] relative to those with normoalbuminuria while acknowledging that albuminuria can regress.[36] Currently, the magnitude of increase in the risk of ESRD for patients with T1DM or T2DM and microalbuminuria is four- to fivefold. Further reductions in CVD, a 'competing' cause of death, may translate to more patients with microalbuminuria living longer and developing ESRD. Microalbuminuria approximately doubles the risk of death from CVD and independently increases the chance that patients die earlier than they would in the absence of albuminuria.[36] Albuminuria may reflect a more general damage to the vascular endothelium. When including albuminuria as a component of overall risk, one can calculate the risk of CVD and death in T2DM.[37]

Existing evidence supports therapies proven to reduce the incidence of CVD, namely BP-lowering drugs (notably those that inhibit the renin–angiotensin system) and statins. Angiotensin blockade lowers the risk of subsequent renal decline, although there is an absence of such evidence in normoalbuminuric, normotensive patients. The beneficial effect of statins in prolonging survival is currently limited to patients without ESRD.[38] With respect to the frequency of testing, the conference work group was aware that annual testing for albuminuria among normoalbuminuric patients has been recommended in diabetes by numerous bodies.[39–43]

The work group considered the following controversies related to testing for albuminuria:

Frequency of screening: The ideal frequency of screening remains undetermined. The work group acknowledged that less frequent screening may result in missed diagnoses but may improve cost-effectiveness.[44]

Albuminuria versus other predictors of further diabetic complications: The work group acknowledged that uncertainty remains about the marginal predictive utility of measuring albuminuria over other CV risk factors.