Cardiovascular Disease and Diabetic Kidney Disease

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Summary: Diabetic kidney disease commonly is associated with an increased risk of cardiovascular disease. There are traditional common risk factors for both conditions including hypertension and poor glycemic control. However, it is likely that there are other pathophysiological mechanisms that explain the clinical phenomenon of increased cardiovascular disease in diabetic patients with chronic kidney and vice versa. Current management of both conditions includes aggressive glucose and blood pressure control. The protective role of treating dyslipidemia has been shown for cardiovascular disease, but the results for renal disease are not as clear. The advent of new classes of glucose-lowering agents such as sodium glucose co-transporter2 inhibitors and glucagon-like peptide-1 agonists has resulted in impressive effects on both cardiovascular and renal disease in diabetes. However, how these drugs act independently of glucose lowering to confer both kidney and cardiovascular protection has not been fully elucidated. Nevertheless, these new treatments provide optimism for reducing both microvascular and macrovascular complications in diabetes, which represent the major causes of morbidity and premature mortality in this condition.
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Diabetes is associated with higher cardiovascular (CV) mortality, with diabetic patients twice as likely to die from vascular causes compared with those without diabetes. Cardiovascular disease (CVD) accounts for more than 60% of the life-years lost from diabetes.[1] Not only is there an increased incidence, but also worse clinical outcomes after CV events among those individuals with diabetes.[2] Indeed, it has been argued that patients with diabetes but without a prior history of myocardial infarction (MI) are as likely to die of CV disease as patients without diabetes who have established coronary artery disease,[3] but this is not a universal finding.[4]

Diabetic kidney disease develops in up to 40% of diabetic patients and is the leading cause of end-stage renal disease (ESRD) worldwide. The impact of chronic kidney disease (CKD) on CV disease increasingly has been recognized as an important cardiovascular risk factor with numerous studies that have reported that reduced glomerular filtration rate (GFR) and albuminuria are the major risk factors for CVD. Patients with CKD are more likely to die from CVD rather than from progression to ESRD. Furthermore, patients who have diabetes and CKD have a disproportionally higher risk for CVD when compared with patients with diabetes who do not have CKD.[5] Most of the excess risk of all-cause and CV mortality for patients with diabetes is related to the presence of diabetic kidney disease (DKD) (Fig. 1). Indeed, this risk is largely limited to the subgroup with kidney disease.[6]

The mechanisms underlying this strong link between diabetic kidney disease and cardiovascular risk are largely unknown. Traditional risk factors that are prevalent among patients with diabetes do not fully account for the heightened risk (Table 1). Despite their enhanced susceptibility, many patients with DKD do not receive the appropriate risk factor modifications that often are provided to the general population. Even when treated to target goals using currently available therapies, there remains a large residual cardiovascular risk for patients with DKD. Furthermore, patients with advanced CKD usually are excluded from large clinical outcome trials, contributing to the evidence gap for treatment of patients with advanced CKD and high cardiovascular risk.

EPIDEMIOLOGY

The increasing prevalence of DKD parallels the dramatic increase in diabetes worldwide. In the year 2015, there were 415 million patients estimated to have diabetes, and for 2040 the prevalence is projected to increase to 642 million, with a disproportionate increase in middle-income countries.[7] The driving force behind this escalating prevalence of diabetes is at least in part the result of the global pandemic of obesity. In the years 1980 to 2000, the overall

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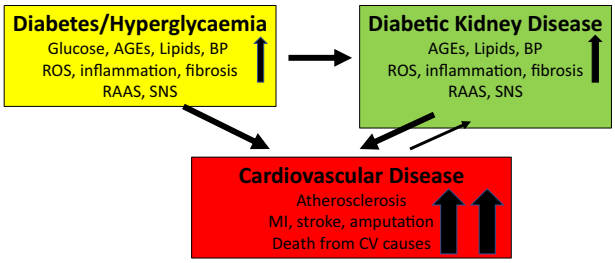

Figure 1. Diabetes and concomitant diabetic kidney disease accelerate cardiovascular disease. AGEs, advanced glycation end products; BP, blood pressure; MI, myocardial infarction; RAAS, renin angiotensin aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system.

prevalence of obesity has increased from 15% to 31%, and now lies between 35% and 40%. Between 1990 to 2012 the number of deaths attributable to CKD increased by 94%.[8,9]

CKD is defined as functional and structural abnormalities of the kidney lasting for 3 months or more, which can either manifest itself as impaired renal function (estimated GFR [eGFR] $\leq$ 60 mL/min/1.73 m^2) or albuminuria/proteinuria. According to the National Health and Nutrition Examination Survey, the number of patients with ESRD has more than doubled from 1991 to 2010, and diabetic nephropathy accounts for approximately 38% of these cases.[5]

CHRONIC KIDNEY DISEASE AND CV DISEASE

As outlined earlier, patients with CKD have an exceptionally high CV risk. For example, in patients with CKD stage 3 (eGFR $\leq$ 60 mL/min/1.73 m^2) the risk of death is more than 10 times higher than the risk of progression to ESRD. Once on dialysis, the 5-year survival is less than 40% in these patients, predominantly owing to CVD-associated morbidity and mortality.[10]

A reduction in eGFR and increased albuminuria have been shown to be independent risk factors for all-cause mortality and CV mortality in the general population.[5] The hazard ratio for death from CV causes increased progressively, with decreasing eGFR. If the eGFR is 45 to 59 mL/min/1.73 m^2 then the hazard ratio for CV death increases to 1.52, and if the eGFR is 15 to 29 mL/min/1.73 m^2 then the hazard ratio reaches 13.51.[5] If the albumin/creatinine level surpasses 10 mg/g, even in the absence of decreased eGFR, the risk for CV mortality increases. Thus, the presence of CKD is a powerful predictor of CV disease, with new clinical guidelines now categorizing CKD patients into the highest risk group for recommendations with respect to prevention, detection, and treatment of CVD.

DIABETES, CV, AND RENAL DISEASE

In a study by Groop et al,[6] a large cohort of more than 4,000 patients with type 1 diabetes was followed up for more than 7 years. The death rate was 7%, which was more than 3.6-fold higher than in the age- and sex-matched general population. Individuals with normoalbuminuria showed no excess mortality independent of the duration of diabetes. The presence of microalbuminuria was associated with a 2.8 higher standardized mortality ratio. Once macroalbuminuria was present the standardized mortality ratio increased to 9.2, and in the presence of end-stage renal disease the standardized mortality ratio was 18.3. Patients with impaired kidney function and individuals showing hyperfiltration had an increased risk of death. Thus, this study has suggested an independent and graded association between the presence and severity of kidney disease and mortality in a large contemporary cohort of individuals with type 1 diabetes. Furthermore, this

Table 1. Traditional and Nontraditional Risk Factors Not Addressed Adequately by Current Treatments

Traditional risk factors for CVD in diabetic patients with DKD
Hyperglycemia
Hyperlipidemia
Hypertension
Heart failure
Atrial fibrillation
Hypercoagulability
Electrolyte disturbances
Nontraditional risk factors for CVD in diabetic patients with DKD
Increased accumulation of AGEs enhanced with interaction with the receptor for AGEs, RAGE
Increased oxidative stress as a result of increased ROS production and reduced antioxidant defense
Inflammation
Endothelial dysfunction
Activation of profibrotic pathways
Activation of the renal and cardiac sympathetic nervous system

AGEs, advanced glycation end products; ROS, reactive oxygen species.