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STAKEHOLDER PERSPECTIVES IN DIABETES MANAGEMENT FOR PATIENTS WITH RENAL IMPAIRMENT

SEPTEMBER 2010 • PART 2 IN A SERIES

Pathophysiology and Measures for Successful Screening and Management of Type 2 Diabetes and Its Associated Complications

By Robyn R. Graham, PharmD, Medical and Managed Care Consultant

The total estimated costs of diabetes in 2007 were \$174 billion, including direct (\$116 billion) and indirect (\$58 billion) expenditures.¹ The cost of diabetes-related chronic complications attributed to diabetes is estimated at \$58 billion.¹ These figures indicate that measures need to be taken to develop effective screening, diagnosis, and monitoring programs to ensure that patients with diabetes achieve glycemic control, which can reduce the incidence of combined major macrovascular and microvascular complications.² An understanding of the pathophysiology of the disease will assist healthcare providers and payers in approaching the management of diabetes with confidence in interventions influencing the change in failed pathophysiologic functions.

The core pathophysiologic defects in type 2 diabetes are insulin resistance in muscle and liver and beta-cell failure.³ These defects are often referred to as the triad of traditional fundamental defects responsible

EDITOR'S NOTE

American Health & Drug Benefits is publishing a newsletter series designed to provide stakeholder insights on diabetes management, chronic kidney disease, and the effect available therapies may have overall. In light of the wealth of published information on diabetes, this newsletter series provides relevant, up-to-date information on diabetes and its related complications, specifically renal impairment, in a clear and concise manner to assist you in the development of innovative policies, practices, and benefit designs to appropriately and effectively manage this complex disease that is associated with exorbitant healthcare costs.

Each newsletter hosts a thought leader whose expert opinion is presented for review and consideration when evaluating diabetes management initiatives. The thought leaders selected for the Editorial Board for this series are respected experts in their respective areas of practice—endocrinology, benefit design, evidence-based medicine, pharmacoeconomics, and nephrology. They provide fair and balanced information to serve as guidance in the choice of appropriate care for patients with diabetes to improve glycemic control; prevent disease progression, including the management of comorbidities, such as chronic kidney disease; and decrease overall healthcare resource utilization and costs.

The first newsletter (available at www.AHDBonline.com) of the series focused on the relevance of diabetes as a topic of substantial relevance to the healthcare industry. This second newsletter is focused on the pathophysiology of diabetes and the many levels of complexity of the disease, which ultimately influence its management and the therapeutic regimen selection. The measurement and screening parameters related to successful diagnosis and management of diabetes and its related complications are also presented. ■

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for the development of type 2 diabetes.⁴ In addition to this triumvirate, fat cells (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/ resistance), alpha-cells (hyperglucagonemia), the kidneys (increased glucose reabsorption), and the brain (insulin resistance) all play pertinent roles in the development of glucose intolerance in patients with type 2 diabetes.^{3,4}

Pathophysiology

Insulin Resistance

Insulin resistance manifests in the liver by an overproduction of glucose during the basal state, regardless of the presence of fasting hyperinsulinemia and an impaired suppression of hepatic glucose production (HGP) in response to insulin, which occurs after a meal.³ Insulin resistance manifests in muscle tissue as impaired glucose uptake after ingestion of a meal that includes carbohydrates, resulting in postprandial hyperglycemia.³

Although the origins of insulin resistance can be traced to the genetic composition of the individual, the diabetes epidemic is related to the epidemic of obesity and overall reduced physical activity.³ Decreased physical activity and obesity are insulin-resistant states.³ These, along with the genetic burden of insulin resistance, result in major stress on the pancreatic beta-cells to augment their secretion of insulin and offset the defect in insulin action.³

Over time beta-cells begin to fail, and initially postprandial plasma glucose levels, and ultimately fasting plasma glucose (FPG) concentrations, begin to rise.³ This failure of beta-cells leads to the onset of overt diabetes.³ Hyperglycemia and poor metabolic control may cause additional decline in insulin sensitivity, but it is the progressive beta-cell dysfunction that determines the rate of disease progression.³

Lipotoxicity

Lipotoxicity refers to the fact that fat cells are resistant to the antilipolytic

effect of insulin in type 2 diabetes, resulting in elevated plasma free fatty acid concentrations and elevated levels of toxic lipid metabolites.⁴ Insulin resistance in muscle and liver result from the toxic lipid metabolites.⁴

Deposition of fat in beta-cells leads to impaired insulin secretion and beta-cell failure.³ Similarly, the hypersecretion of islet amyloid polypeptide (cosecreted in a 1:1 ratio with insulin) can lead to progressive beta-cell failure.³

Incretin Hormones

The role of incretin hormones and their contribution to the pathophysiology of diabetes has become more apparent in the past few years.⁵ Incretins are gut-derived peptide hormones, principally glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide.^{6,7} These hormones are secreted at low basal levels in the fasting state, with circulating levels increasing rapidly after food ingestion.⁶

GLP-1 has several glucoregulatory actions that work in a glucose-dependent manner—enhancement of endogenous insulin release and suppression of inappropriate glucagon secretion, thereby augmenting glucose-induced insulin secretion in a highly glucose-dependent manner.^{5,7} GLP-1 also regulates gastric emptying and has the ability to slow gastric emptying, which is often accelerated in type 2 diabetes.^{4,5} GLP-1 increases satiety and decreases appetite and therefore food intake.^{4,5}

Glucagon

Glucagon plays an important role in the maintenance of the majority of basal HGP in patients with type 2 diabetes.⁴ Even in the presence of hyperglycemia and hyperinsulinemia, which should suppress glucagon secretion, plasma glucagon concentrations are elevated in individuals with impaired glucose tolerance and type 2 diabetes compared with those who have normal glucose tolerance.⁴ Alpha-cells produce glucagon

in response to low blood glucose levels, serving a counterregulatory function.⁸

Increased pancreatic alpha-cell secretion results in elevated concentrations of glucagon, which enhance HGP and aggravate the hepatic insulin resistance.⁴ Type 2 diabetes is characterized by fasting hyperglucagonemia and by a failure to suppress glucagon, partially driven by alpha-cell insensitivity to a rise in blood glucose.⁸

Renal Glucose Reabsorption

The kidney filters approximately 162 g of glucose daily, 90% of which is reabsorbed by the high-capacity sodium-dependent glucose (co)transporter (SGLT)-2 in the convoluted segment of the proximal tubule.³ The remaining 10% of the filtered glucose is then reabsorbed by SGLT-1 in the straight segment of the descending proximal tubule.³ The result of this reabsorption process is the absence of glucose in the urine.³ In patients with type 2 diabetes, an adaptive response by the kidney to conserve glucose, which is essential to meet the energy requirements of the body, becomes maladaptive.³ When this occurs, the kidney, instead of dumping glucose in the urine to correct the hyperglycemia, retains the glucose.³ Furthermore, the ability of the diabetic kidney to reabsorb glucose appears to be amplified by an absolute increase in the renal reabsorptive capacity for glucose.³

Brain Involvement

It is evident that the obesity epidemic is influencing the current epidemic of diabetes.³ Obese individuals with type 2 diabetes, and those without it, are characterized by insulin resistance and compensatory hyperinsulinemia³—the beta-cell increases secretion of insulin to compensate for insulin resistance.⁴ Under normal conditions, insulin signals the brain to stop eating and reduce energy intake, but in obese individuals, even in the presence of hyperinsulinemia (which should cause appetite suppression), food intake is increased.^{3,4} This indicates that

the appetite centers in the brain are resistant to insulin.⁴

Clinical Implications of Pathophysiology

What is the significance of the pathophysiology of diabetes? Why do we emphasize it? DeFronzo stated that the ominous octet dictates the requirement of multiple drugs used in combination to treat type 2 diabetes.³ DeFronzo outlines the following therapeutic implications of the pathophysiology of type 2 diabetes³:

- Effective treatment of type 2 diabetes will require combination use of multiple drugs to correct the multiple pathophysiologic defects
- Treatment should not be based simply on the reduction of hemoglobin A_{1c} levels but on the known pathogenic abnormalities
- If progressive beta-cell failure is to be prevented, therapy must be initiated early in the natural history of type 2 diabetes.

Information on the management of type 2 diabetes will be discussed in subsequent newsletters. The current newsletter emphasizes screening and diagnosis of diabetes in addition to providing an overview of diabetes-related renal impairment.

Screening and Diagnosis Measures

Screening to detect prediabetes and diabetes in asymptomatic individuals should be considered in overweight and obese adults, regardless of age, and in those who have 1 or more additional risk factors for diabetes.⁹ Screening should begin at age 45 years for individuals without risk factors, and at a minimum of 3-year intervals subsequently.⁹

Once a diagnosis of prediabetes has been made, monitoring for the development of diabetes should be done annually.⁹ The measures for screening and for diagnosing type 2 diabetes are the same.⁹

The **Table** summarizes the measures for screening and diagnosing prediabetes and diabetes, as well as recommendations for monitoring patients. The objective is

Table. Measures for Diabetes Screening, Diagnosis, and Monitoring

Screening/diagnosis of prediabetes	Screening/diagnosis of diabetes	Monitoring postdiagnosis
IFG FPG 100 mg/dL-125 mg/dL ^a	FPG ≥126 mg/dL (7.0 mmol/L) ^{a,b}	SMBG Exact recommendations are unclear, but it may be useful as a guide to the success of therapy ^a
IGT 2-h plasma glucose 140 mg/dL-199 mg/dL ^a	Casual plasma glucose ≥200 mg/dL + classic symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) ^{a,b}	HbA _{1c} Twice yearly: patients who meet glycemic goals ^a Quarterly: patients whose therapy has changed or who do not meet glycemic goals ^a As needed: point-of-care testing for timely decisions on therapy changes ^a
	2-h plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test ^{a,b}	

^aAmerican Diabetes Association. *Diabetes Care*. 2010;33(suppl 1):S11-S61.
^bRodbard RW, et al. *Endocr Pract*. 2007;13(suppl 1):1-68.
 FPG indicates fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA_{1c}, glycolated hemoglobin; SMBG, self-monitored blood glucose.

to follow these recommendations to identify and intervene early to delay disease progression and long-term complications associated with the pathogenic disturbances underlying type 2 diabetes.⁴

Diabetes, Kidney Disease, and Costs

The American Diabetes Association has reported that renal impairment contributes to 29% of diabetes-associated expenditures.¹ The United States Renal Data System (USRDS) 2009 Annual Report indicates that the prevalence of chronic kidney disease (CKD) is on the rise, which is influencing associated costs.¹⁰ Expenditures related to CKD increased from 10.8% of total Medicare spending in 1993 to 27.6% in 2007.¹⁰ Unlike end-stage renal disease, however, there is no registration system for CKD, thus the CKD-related expenditures may be underestimated.¹⁰

The USRDS reports that the overall per member per month (PMPM) costs reach \$2002 and \$2531 for Medicare patients with CKD and the younger

patients with CKD in the MarketScan database, respectively.¹⁰

Of note, in Medicare beneficiaries, expenditures are approximately 4 times greater in those with CKD plus diabetes and cardiovascular disease than in patients with CKD alone—\$2558 compared with \$688 respectively.¹⁰ A similar finding was reported for the younger MarketScan database population with each of the 3 diseases, for whom the PMPM costs rise to \$4400, 3 times that of the \$1379 incurred by patients with CKD alone.¹⁰ Noting these data, the USRDS stated that using simple biochemical tests to identify CKD would provide an opportunity for healthcare providers to target at-risk populations for active interventions.¹⁰

The considerable contribution of renal impairment to diabetes,¹ and the USRDS data, indicate a significant economic burden resulting from patients with diabetes and CKD. So what is the relationship between diabetes and CKD?

In most patients with diabetes, CKD should be considered attributable to

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diabetes when macroalbuminuria is present, or when microalbuminuria is present in the presence of diabetic retinopathy.¹¹

In the absence of diabetic retinopathy, low or rapidly decreasing glomerular filtration rate (GFR), rapidly increasing proteinuria or nephrotic syndrome, refractory hypertension, presence of active urinary sediment, signs or symptoms of other systemic disease, or >30% reduction in GFR within 2 to 3 months after initiation of an angiotensin-converting enzyme inhibitor or of an angiotensin receptor blocker, causes of CKD other than diabetes should be considered.¹¹

The Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines include a summary of the likelihood of diabetic kidney disease according to staging by GFR and level of albuminuria.¹¹ It appears that patients are most likely to develop diabetic kidney disease when macroalbuminuria is present with any degree of renal impairment and GFR between <30 mL/min (stages 4 and 5) and >60 mL/min (stages 1 and 2).¹¹

It is important to emphasize the relationship between diabetes and any degree of renal impairment, because renal function plays a significant role in both the pathophysiology of diabetes and the general well-being of patients once they are diagnosed with diabetes and complications begin to arise. According to the KDOQI clinical practice guidelines, any degree of renal impairment can be considered diabetic kidney disease, depending on the level of albuminuria.¹¹

Therefore, healthcare providers and managed care organizations (MCOs) need to make it a point to join forces to increase awareness and educate patients and members on early screening and the necessity to begin monitoring renal function at the time prediabetes or diabetes is diagnosed and at the suggested intervals presented in the first newsletter in this series.

CKD Awareness and Screening

Plantinga and colleagues used National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 to assess patient awareness of CKD stages 1 through 4.¹² Of the 2992 participants who had CKD stages 1 through 4, only 6% reported being told that they had weak or failing kidneys.¹² Even in the participants with stage-4 CKD, <50% were aware that they had any degree of renal impairment.¹² Similarly, Giannelli and colleagues estimated the magnitude of misclassification of renal function in persons with normal serum creatinine who have reduced GFR.¹³ Although participants in the study had normal serum creatinine values, only 8% of the population aged ≥65 years had normal renal function (ie, GFR >90 mL/min). More than one third (39%) of the population had moderate renal function (ie, GFR 30-59 mL/min), and 25% had a GFR <60 mL/min.¹³

These findings emphasize that relying on normal serum creatinine alone as evidence of normal renal function will result in missing moderate renal impairment in a substantial proportion of the population older than age 65.¹³ This is not something to take lightly, because patients with a sustained GFR <60 mL/min for 3 months would meet the criteria for CKD.¹³ If patients are misclassified, treatment decisions and outcomes may be impacted.

Kennedy and colleagues assessed the use of serum creatinine to measure renal function in patients taking metformin.¹⁴ In their study, >75% of the patients were treated by primary care physicians or other nonendocrinologists.¹⁴ In addition, Kennedy and colleagues suggested that the proportion of patients taking metformin who have any degree of renal impairment might be larger than previously thought if GFR is used in place of serum creatinine.¹⁴ These data suggest that it may not be good practice to rely solely on serum creatinine for the

determination of renal impairment,¹⁴ and it is important to consider renal function when evaluating treatment options in patients with type 2 diabetes, because many of the therapeutic options for type 2 diabetes are associated with risk when used in patients with renal impairment.¹⁵

Another study helps to further emphasize the significance of renal impairment in patients with prediabetes, those with diabetes, and those without diabetes. Using NHANES data from 1999 to 2006, Plantinga and colleagues estimated and compared the community prevalence of CKD among people with diagnosed diabetes (self-reported), undiagnosed diabetes (ie, FPG ≥126 mg/dL), prediabetes (ie, FPG ≥100 mg/dL), and no diabetes (ie, FPG <100 mg/dL).¹⁶ The prevalence of CKD by diabetes status was identified to be¹⁶:

- Undiagnosed diabetes: 41.7%
- Diabetes: 39.6%
- Prediabetes: 17.7%
- No diabetes: 10.6%.

Not only was the prevalence of CKD high in patients with diabetes, but the stage of CKD (stage 3 or 4) was advanced in 39.0%, 40.6%, and 56.2% of the patients with diabetes, undiagnosed diabetes, and prediabetes, respectively.¹⁶

These findings indicate that awareness and screening for any degree of renal impairment needs to be increased and accomplished early in all patients, especially in those with type 2 diabetes. The KDOQI is a very useful resource for providers and MCOs to reference when trying to increase the awareness of diabetes and CKD and provide education on the significance and importance of adherence to therapy and management of diabetes and CKD.¹¹

Conclusion

Diabetes is a chronic illness that requires vigilance in medical care to prevent acute complications and reduce the overall risk of long-term complications.⁹ The pathophysiology of diabetes is multifaceted and complex, and

the management of diabetes is a complex task that cannot be taken lightly.

In this newsletter, we briefly reviewed the screening and diagnosis of diabetes and related CKD. Future newsletters will outline the overall management of type 2 diabetes specifically in relation to its comorbidities, such as renal impairment. Please join us on a journey to disclose pertinent details of the management of type 2 diabetes and its related complications. ■

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Robyn R. Graham, PharmD, is a consultant in the pharmaceutical and managed care industries. Dr Graham is former Pharmacy Program Coordinator for Humana Health Plans and former Regional Director of Clinical Programs for United-Health Group, where she worked with the pharmacy management team at Diversified Pharmaceutical Services (now Express Scripts) on disease management, health and wellness initiatives, outcomes measurement, and preferred drug list/pharmacy benefit implementation. She is a member of the Academy of Managed Care Pharmacists and the American Society for Healthcare Risk Management.

STAKEHOLDER PERSPECTIVE

Significance of Early Identification of Diabetic Kidney Disease

By Adam Whaley-Connell, DO, MSPH, Assistant Professor of Medicine, Division of Nephrology and Hypertension, Harry S. Truman VA Medical Center and the University of Missouri-Columbia School of Medicine, Columbia, MO

Chronic kidney disease (CKD) is increasingly common and affects approximately 24 million to 28 million people in the United States, with an approximate 20 million more unidentified or at risk.^{1,2} With the exponential growth of type 2 diabetes mellitus, the leading cause of incident CKD and end-stage renal disease (ESRD), it has become evident that CKD is now a global public health problem.³ Indeed, CKD progression to ESRD is increasing in incidence and prevalence worldwide in addition to an increasing recognition that management of diabetic-related CKD is critical in delaying progression to ESRD and related complications.⁴

Likewise, CKD in patients with diabetes augments cardiovascular disease

(CVD), which is the leading cause of morbidity and mortality associated with diabetes.^{3,5,6} Improving individual CVD risk is the foremost concern in the management of this population.^{5,7} There are several interventions to delay progressive loss of renal function and/or reduce development of CVD. However, awareness of CKD is low, and disease progression is asymptomatic; hence, the majority of patients either do not survive it, or CKD is detected only shortly before the onset of symptomatic uremia, when opportunities to prevent adverse CVD outcomes are few.^{6,8,9} Intervention in early-stage CKD is, therefore, likely to be more effective in delaying disease progression and improving diabetic-related CKD morbidity and mortality.⁸

The Importance of Screening for Early-Stage CKD

With the recognition that incident and prevalent CKD is increasing,⁴ the primary focus of current practice guidelines is to promote screening and detection of CKD in early stages so that appropriate interventions to prevent progression of kidney disease can be undertaken.³ Several initiatives—such as the National Kidney Foundation (NKF)-sponsored Kidney Early Evaluation Program,¹⁰ the National Institutes of Health Healthy People 2010,¹¹ and the Kidney Disease Education Program¹²—have taken the lead in educating patients as well as healthcare professionals about CKD and diabetic kidney disease (DKD) and its implications, and the positive

impact of early screening and treatment.

The Kidney Disease Outcomes Quality Initiative (KDOQI),⁶ Kidney Disease: Improving Global Outcomes (KDIGO),¹³ and the American Diabetes Association¹⁴ clinical practice guidelines recommend screening and stratifying at-risk individuals for CKD using blood pressure, estimated glomerular filtration rate (eGFR) based on serum creatinine (sCr) and other variables, urine albumin-to-creatinine ratio, examination of the urine sediment for red blood cells and white blood cells and casts, and imaging studies of the kidneys (in select individuals at increased risk of developing CKD).^{6,13,14} Those identified as being at highest risk are those with diabetes, hypertension, autoimmune diseases, patients recovering from an episode of acute renal failure, or those with a family history of CKD.⁶

Detection of Early-Stage CKD

The most common markers used in clinical practice for detection of CKD are sCr, eGFR, and proteinuria.⁶ Although sCr is a readily available test used in clinical practice to assess renal function, its results vary with age, sex, muscle mass, and diet. As a result, the use of sCr may not give an accurate estimate of the kidney function. However, when sCr is used to calculate an estimated GFR, it is considered one of the best overall measures of renal function and can be used as a screening tool for the diagnosis, staging, and monitoring of CKD.

The traditional method of estimating GFR values by calculating creatinine clearance from a timed (usually 24-hour) urine collection is cumbersome. To overcome this, eGFR values can now be calculated from prediction equations that take into account sCr, as well as other variables, such as age, gender, race, and body size.¹⁵⁻¹⁷ The equations most often used for eGFR in adults are the Cockcroft-Gault,¹⁵ the US Modification of Diet in Renal Disease,¹⁶ and the recent CKD-epidemiology collaboration equations.¹⁷

In the United States, diagnosis and

classification of CKD are based on a set of established clinical practice guidelines—the 2002 NKF-KDOQI and the 2005 KDIGO guidelines.^{6,13} Based on these guidelines, CKD is defined as 1 of 2 options^{6,13}:

1. Kidney damage ≥ 3 months, as confirmed by kidney biopsy or by markers of kidney damage (ie, presence of structural or functional abnormalities as evidenced by abnormal blood, urine, or imaging studies) with or without a decrease in GFR, or

2. GFR < 60 mL/min/1.73 m² for ≥ 3 months, with or without kidney damage. CKD is then stratified by risk into stages 1 to 4 based on the level of GFR, with declining GFR being associated with worsening CKD. GFR < 15 mL/min/1.73 m² is considered stage 5 CKD/ESRD.

When using eGFR > 60 mL/min/1.73 m² for the diagnosis and detection of CKD at earlier stages, the presence of proteinuria is required to meet the diagnosis.^{6,13} The KDOQI and KDIGO work groups advocate under most circumstances untimed (“spot”) first morning void urine samples to detect and monitor proteinuria in children and adults.^{6,13} Although random sampling and even dipsticks are acceptable, individuals who test positive should undergo confirmation.⁶ Monitoring should then be performed using quantitative measurements of protein (or albumin)-to-creatinine ratio in spot urine samples and in general are stratified based on risk; 30 mg/g-300 mg/g to diagnose microalbuminuria and > 300 mg/g to diagnose macroalbuminuria or overt proteinuria.^{6,13}

Proteinuria is considered a marker for kidney injury and has been shown over time to be a strong marker/predictor of cardiovascular outcomes, as well as kidney disease progression.⁶ The KDIGO international work group readdressed this important point in 2009 at a conference dedicated to the controversies in definition, classification, and prognosis of CKD.¹³ Central to the discussion is a

strong understanding from recent data that CKD and other high-risk conditions (eg, hypertension and diabetes) are increasing and, accordingly, so is CVD morbidity and mortality associated with CKD.¹⁸ The KDIGO work group recently reached a consensus on CKD staging based on the need for improvements in prediction of prognosis for CKD that could be improved by including proteinuria and eGFR measures, along with the cause of disease (eg, diabetes and hypertension) in the classification scheme.^{18,19} The work group, however, did not advocate to change the definition but rather opted to modify and include proteinuria and the cause of disease. It is anticipated the NKF-KDOQI will address this and issue a new set of guidelines in the near future.

Early-Stage CKD a Risk Factor for CVD

The most common risk factors for incident and prevalent CKD include type 2 diabetes, obesity, and hypertension.¹ In the context of early-stage CKD (eg, eGFR > 60 mL/min/1.73 m² and the presence of proteinuria), diabetes- and hypertension-related kidney disease often accompany other comorbid conditions, particularly the other traditional Framingham CVD risk factors—dyslipidemia, tobacco use, and increasing age.²⁰ In addition, the presence of CKD can be associated with nontraditional CVD risk factors, such as mineral metabolism disorders, anemia, uremia, oxidative stress, and inflammation.^{6,20,21} However, these comorbid conditions largely occur at more advanced stages, especially as GFR diminishes to < 60 mL/min/body surface area. The collective weight of these comorbid conditions contributes to overall high morbidity and mortality associated with CKD.²⁰ It is therefore widely considered that therapeutic interventions, as well as pharmacologic and lifestyle modifications, are imperative to reducing cardiovascular risk, as well as kidney disease progression in early-stage CKD.

The traditional measured outcomes of

CKD include progression of CKD (doubling of sCr); progression to ESRD; CVD morbidity and mortality and development of complications of impaired kidney function (eg, eGFR <60 mL/min/1.73 m²), such as anemia, disorders of mineral metabolism, and secondary hyperparathyroidism. The correlation between raised sCr levels and CVD mortality was first observed in 1989 by Shulman and colleagues in the Hypertension Detection and Follow up Program study.²² This concept received wide attention in 2003 after the scientific statement from the American Heart Association (AHA) endorsed the finding that increased CVD mortality is noted in patients with CKD compared with the general population.²¹ There is a strong, continuous correlation between increased risk for CVD events and impaired renal function, which begins at the earliest stages of renal impairment and rises continuously to 20 to 30 times above the risk in the general population as renal damage progresses to ESRD.²¹ Although the risk for CVD morbidity and mortality is evident at eGFR <60 mL/min/1.73 m², increasing sharply when eGFR is <45 mL/min/1.73 m², the evidence for this begins with an eGFR <90 mL/min/1.73 m²,¹⁸ and is strongest at early stages of CKD when weighted with proteinuria.²¹

The Importance of Diabetes in Early-Stage CKD and CVD

Type 2 diabetes mellitus is a growing worldwide epidemic affecting at least 171 million people.²³ As a result, diabetic complications, such as CKD and CVD, represent grave public health threats.^{20,24,25} Numerous studies have described a similar relationship in patients with early-stage CKD; the presence of type 2 diabetes augments prevalent CVD compared with those without diabetes.^{6,20}

The role of diabetes in early-stage CKD, especially in the context of CVD morbidity and mortality, is highlighted when considering the notion that proteinuria at an eGFR >60 mL/min/1.73 m²

strengthens predictors of kidney disease progression and CVD events.⁷ Many studies have demonstrated a continuous, graded relationship between increasing levels of proteinuria and prevalent risk factors for CVD events, including insulin resistance, hypertension, obesity, and dyslipidemia,^{21,26} which are especially pronounced in the presence of lower level proteinuria or microalbuminuria, a finding characteristic of early-stage CKD.

Therefore, the presence of ≥1 of the traditional CVD risk factors with microalbuminuria, such as hypertension, obesity, dyslipidemia, tobacco use, and/or advanced age, convey a significant increased risk for CVD mortality in diabetic patients with early-stage CKD.^{9,20,21,26}

Given the enormous CVD risk burden observed in patients with CKD, especially in those with diabetes, multiple work groups have convened to address CVD in CKD. Current practice should dictate that patients with CKD, even at early stage, be considered in the “highest risk group” for subsequent CVD events, as recommended by the AHA,²¹ as well as by complementary statements from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)²⁷ and the NKF.⁶ As a result, those with early-stage CKD (eGFR >60 mL/min/1.73 m²) and demonstrated proteinuria should be treated as a coronary artery disease equivalent for purposes of risk stratification.²¹

Conclusions

It is well recognized that incident and prevalent CKD is increasing, along with the growth of diabetes.⁹ In this context, the burden of CKD morbidity and mortality is high, an observation that extends into the earliest stages of CKD and that is augmented by the presence of diabetes. Management of early-stage CKD/DKD is critical in delaying progression, as well as CKD-related complications, and several interventions are now available. However,

awareness and identification of CKD remains low. Managed care organizations and healthcare professionals can and should work together to increase awareness of CKD and ensure that screening programs are effectively implemented in at-risk populations. Ultimately, aggressive screening programs will prevent or delay the further development of CKD to more advanced stages, which will help decrease overall healthcare expenditures related to CKD/DKD and improve the quality of life of this patient population, as well as decrease the burden on their caregivers. ■

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About the Author of the Perspective

Adam Whaley-Connell, DO, MSPH, is an Assistant Professor of Medicine in the Division of Nephrology and Hypertension at the Diabetes and Cardiovascular Center of Excellence, University of Missouri-Columbia School of Medicine, and the Harry S. Truman VA Medical Center. Dr Whaley-Connell is responsible for the hypertension clinics at the university. He heads a research program funded through



the National Institutes of Health and the Veterans Administration that centers on metabolic kidney disease, with a focus on the renin-angiotensin-aldosterone system. Dr Whaley-Connell is an internationally recognized expert on diabetic kidney disease and has published approximately 150 professional articles in many peer-reviewed publications on hypertension and diabetes-related topics.

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