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National Kidney Foundation consensus conference on cardiovascular and kidney diseases and diabetes risk: an integrated therapeutic approach to reduce events

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Cardiovascular disease (CVD) is the most common cause of death in industrialized nations. Type 2 diabetes is a CVD risk factor that confers risk similar to a previous myocardial infarction in an individual who does not have diabetes. In addition, the most common cause of chronic kidney disease (CKD) is diabetes. Together, diabetes and hypertension account for more than two-thirds of CVD risk, and other risk factors such as dyslipidemia contribute to the remainder of CVD risk. CKD, particularly with presence of significant albuminuria, should be considered an additional cardiovascular risk factor. There is no consensus on how to assess and stratify risk for patients with kidney disease across subspecialties that commonly treat such patients. This paper summarizes the results of a consensus conference utilizing a patient case to discuss the integrated management of hypertension, kidney disease, dyslipidemia, diabetes, and heart failure across disciplines.

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KEYWORDS: cardiovascular; diabetes; nephropathy

ILLUSTRATIVE CASE

This 58-year-old non-smoking obese man presents 1 week after hospital discharge for the treatment of heart failure. Hospital stay revealed left ventricular hypertrophy, diastolic dysfunction, with left ventricular systolic ejection fraction of 50% by echocardiogram, and no evidence of myocardial ischemia. He feels well. The past medical history includes type 2 diabetes, hypertension, and dyslipidemia treated with ramipril 5 mg, furosemide 40 mg, metoprolol XL 25 mg, metformin 1 g, and atorvastatin 20 mg (all daily). Physical exam: blood pressure (BP) 152/92 mm Hg, P 68/min and regular, and body mass index 33. Jugular venous pressure is not visible. Heart rate is regular with S1 and S2 and no gallop. Lung exam reveals bibasilar rales. There is +1 peripheral edema. Data are shown in Table 1. Screening results for anemia, and mineral and bone disorder are unremarkable (data not shown).

BP TARGETS AND VASCULAR INJURY IN CHRONIC KIDNEY DISEASE (CKD)

Outcomes cardiovascular and kidney disease progression

BP values >140/90 mm Hg are associated with higher risk for adverse kidney and cardiovascular outcomes.¹ The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) hypertension guideline level of evidence is A: angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for proteinuric individuals, B: target <130/80, and C: proteinuria attenuation as a goal of therapy.² The optimal lower BP target is not clearly established as the trial evidence is limited by the failure of most studies to achieve <130/80 for patients with diabetes and/or CKD, as recommended by Joint National Committee 7,¹ American Diabetes Association,³ and KDOQI guidelines,² for slowing the loss of kidney function and improving cardiovascular disease (CVD) outcomes. However, most of the studies showed that the

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Table 1 | 58-Year-old non-smoking obese man with heart failure in the setting of type 2 diabetes, hypertension with preserved left ventricular function, and dyslipidemia

| Vignette data | Discharge | Week 1 | Week 3 | Week 5 |
|--|---|---------------------------------------|--|-------------------------------------|
| Blood pressure | 138/88 | 152/92 | 138/86 | 134/84 |
| eGFR (ml/min per 1.73 m ²) | 45 | 43 | 40 | 34 |
| Fasting serum test | | | | |
| Creatinine (mg/dl) | 1.6 | 1.6 | 1.7 | 2.0 |
| Potassium (mEq/l) | 3.8 | 5.0 | 3.8 | 4.1 |
| Cholesterol (mg/dl) | 188 | | | |
| HDL (mg/dl) | 32 | | | |
| LDL (mg/dl) | 112 | | | |
| Triglycerides (mg/dl) | 220 | | | |
| Glucose (mg/dl) | 188 | 120 | 136 | 120 |
| Hemoglobin A1c (%) | | 6.7 | | |
| Urinary test | | | | |
| Albumin-creatinine ratio (mg/g) | 480 | | 360 | 300 |
| Intervention | | | | |
| Prescribed treatment | Ramipril 5 mg, furosemide 40 mg, metoprolol XL 25 mg, metformin XL 1 g, atorvastatin 20 mg (all once daily) | Increase furosemide 40 mg twice daily | Increase ramipril 10 mg, substitute glipizide 10 mg for metformin (all once daily) | Add spironolactone 25 mg once daily |

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density cholesterol; LDL, low-density cholesterol.

achieved systolic BP (SBP) target predicts loss of kidney function. In addition, for patients over the age of 50, the SBP is the best predictor of myocardial infarction, heart failure, and stroke. Lastly, the target of <130/80 does not address the risks of overtreatment. A meta-analysis of 61 observational studies, including one million adults with no pre-existing CVD, did demonstrate that risk for cardiovascular events doubles for every systolic/diastolic 20/10 above a BP of 115/75.⁴ However, in two prospective studies that randomized subjects without diabetes to different levels of BP reduction, the African American Study of Kidney Disease (AASK)⁵ and the Ramipril Efficacy in Nephropathy-2 (REIN-2) study,⁶ neither kidney disease progression nor CVD risk was reduced at the lower target (mean arterial pressure \leq 92 in AASK and <130/80 in REIN-2). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed no effect of an intensive target SBP <120 versus SBP <140 on CVD outcomes.⁷

A practical approach targets a sitting SBP of 130 or less if tolerated, including assessment of symptoms of orthostatic hypotension. In addition, current evidence supporting albuminuria as a therapeutic target is reviewed in detail elsewhere.⁸ Methods of monitoring BP are described in Table 2.⁹⁻¹³

Drug therapy in CKD

The diagnosis of CKD should influence the selection and sequence of antihypertensive agent use.^{1,2} By the time individuals develop impaired kidney function, three or more drugs are generally needed to achieve BP targets. Overall, attaining BP targets receives less attention in the literature and is arguably more important than selection of individual agents.

Renin-angiotensin-aldosterone system (RAAS) blockade

Studies in diabetic nephropathy demonstrate that the greater the initial decrease of kidney function with RAAS blockade,

Table 2 | Methods of blood pressure measurement

| Method | Advantages | Disadvantages |
|--|--|--|
| Office/clinical blood pressure measurement | Most commonly used in RCTs and long-term outcome trials | Highly variable, observer bias, white-coat HTN |
| HBPM | Improves patient compliance and hypertension control rates | Requires training and device calibration |
| ABPM | Detection of white-coat and masked HTN | Not commonly reimbursed by all health insurers |
| | Wide availability and low cost | |
| ABPM | Only way to assess non-dipping (common in CKD) | Availability |
| | Detection of white-coat and masked HTN | |

Abbreviations: ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; HBPM, self-home blood pressure monitoring; HTN, hypertension; RCTs, randomized controlled trials.

the greater the long-term preservation of kidney function.¹⁴ Consequently, an initial limited loss of estimated glomerular filtration rate (eGFR) following the initiation of RAAS blockade is not a concern unless it exceeds 30–50%, in which case states predisposing to excessive eGFR responses to RAAS blockade such as diuretic-induced hypovolemia or renal artery stenosis should be considered.^{2,15,16} If these conditions are not present, RAAS blockade should be continued. In addition to concern about the initial decrease of eGFR after RAAS blockade, another common misconception is the notion that RAAS blockade should be avoided if kidney function is impaired. Nevertheless, when initiating RAAS blockade, the clinician and the patient should be aware of potential side effects associated with this therapy, e.g., hyperkalemia, cough, angioedema, and anemia. Because of the association between increases in albuminuria and CKD

progression,¹⁷ it is important to monitor albuminuria before and after onset of RAAS blockade to achieve optimal attenuation. High-sodium intake further exacerbates pre-existing albuminuria and increases CKD progression.¹⁸

If urinary albumin-creatinine ratio is not decreased by at least >30% below initial levels where treatment was initiated or to <300 mg/g, in spite of BP levels <130/80 on a low-sodium diet, consideration should be given to addition of either a different class of RAAS blocker or possibly diltiazem.¹⁹⁻²¹

The evidence for the combination RAAS blocking therapy for proteinuria reduction is currently limited to a meta-analysis of 49 small, variable quality studies wherein proteinuria reduction was assessed against a dihydropyridine calcium channel blocker, thus, favoring the ACEi and ARB.²² The renal outcomes with telmisartan, ramipril, or both in people at high vascular risk (ONTARGET) study demonstrated no benefit of the ACEi/ARB combination arm versus either the ramipril 10 mg daily or telmisartan 80 mg daily groups on initiation of chronic dialysis.²³ In contrast, the combination did significantly lower proteinuria versus either form of monotherapy. An important caveat is that the majority of the patients enrolled in the trial did not have albumin-creatinine ratio \geq 300 mg/g.²⁴

Although the potassium sparing diuretics, spironolactone, and epleronone have been shown to reduce proteinuria, there are no kidney outcome data,²⁵ and their addition to ACEi or ARB increases the risk of hyperkalemia. This hyperkalemia risk is predominantly seen, however, among those with an eGFR <45 ml/min per 1.73 m² along with a baseline potassium of >4.5 mEq/l when already on an appropriate diuretic and maximal dose RAAS blocker.²⁶ Thus, the role of these agents is not established. In addition, the direct renin inhibitor, aliskiren, reduced proteinuria in one recent trial when added to an ARB.²⁷ Similarly, its role is not established. In non-proteinuric patients, there is little definite evidence for the superiority of the RAAS blockade over other antihypertensive medications, except in the AASK trial, and in light of the ONTARGET trial, combination ACEi/ARB therapy should be avoided in patients with albumin-creatinine ratio <300 mg/g.

Failure to attain BP target

If BP remains uncontrolled on three or more drugs given in maximally effective and tolerated doses, the patient should be referred to a hypertension specialist or nephrologist. The main causes are insufficient diuretic treatment or failure to restrict excessive sodium intake, non-adherence to medications, or other medications such as nonsteroidal anti-inflammatory drugs-induced sodium retention, and obstructive sleep apnea.¹ Table 1 describes the patient's course and drug interventions received.

THE IMPACT OF DYSLIPIDEMIA MANAGEMENT ON ATHEROSCLEROSIS PROGRESSION IN CKD

Introduction

Most patients with diabetes and CKD have dyslipidemia and are at particularly high risk for macrovascular complications,

especially in the presence of albuminuria.^{28,29} As eGFR declines, high-density cholesterol falls, and some data suggest association of dyslipidemia with more rapid loss of kidney function. Current guidelines recommend statin therapy for low-density cholesterol (LDL) >100 mg/dl together with therapeutic lifestyle changes.²⁸⁻³⁰ Patients with diabetes and CKD typically have low high-density cholesterol, hypertriglyceridemia, and average LDL; LDL particles in people with diabetes tend to be smaller, denser, and possibly more atherogenic.³¹⁻³⁵ Therefore, CKD patients are high priority candidates for treatment of dyslipidemia. Modifying CVD risk by using lipid-lowering agents is a cost-effective strategy in people with type 2 diabetes.³⁶

LDL-lowering therapy and risk of CVD in diabetes and CKD stages 1 to 3

Primary and secondary prevention trials, including those in people with diabetes evaluating different statins, have documented substantial cardiovascular benefit.^{37,38} The recent primary prevention Collaborative Atorvastatin Diabetes Study reported an impressive decrease in cardiovascular deaths in people with type 2 diabetes in the absence of markedly decreased kidney function.³⁹ In terms of absolute risk reduction, patients in the Heart Protection Study with diabetes and CVD received the greatest benefit from statin therapy.⁴⁰

A *post hoc* analysis of data from the Pravastatin Pooling Project, a subject-level database combining results from three randomized trials of pravastatin, 40 mg daily, versus placebo, included 19,737 subjects, of whom 4099 (20.8%) had CKD, but not diabetes, at baseline; 873 (4.4%) had diabetes, but not CKD; and 571 (2.9%) had both conditions.⁴¹ The incidence of the primary composite CVD outcome was lowest in individuals with neither CKD nor diabetes (15.2%), intermediate in subjects with only CKD (18.6%) or only diabetes (21.3%), and highest in subjects with both comorbid conditions (27.0%). Pravastatin significantly reduced the risk of the primary outcome by 25% in subjects with CKD and comorbid diabetes and by 24% in subjects with either characteristic. The absolute reduction in risk of the primary outcome because of pravastatin use was highest in subjects with both CKD and diabetes (6.4%) and lowest in subjects with neither characteristic (3.5%). This study provides indirect evidence that pravastatin treatment effectively decreases the risk of CVD in diabetes with CKD stages 1 to 3. The Treating to New Targets study investigated the effects of intensive lipid-lowering with atorvastatin 80 versus 10 mg daily in ~10,000 patients (15% diabetes) with coronary heart disease with and without pre-existing CKD for a median follow-up of 5 years.^{42,43} CKD was defined solely on the basis of eGFR <60 ml/min per 1.73 m² in 3107 patients. The patients with CKD randomized to 80 mg atorvastatin daily experienced 32% fewer cardiovascular events (hazard ratio (HR) = 0.68; 95% confidence interval (CI): 0.55-0.84; *P* = 0.0003) compared with those with CKD treated with the 10 mg daily dose.⁴³ In addition, a secondary analysis of

3267 patients with stage 3 CKD predominantly who were randomized to rosuvastatin 20 mg daily or placebo in the JUPITER (Justification for the Use of Statins in Prevention—an Intervention Trial Evaluating Rosuvastatin) trial revealed 45% reduction in risk of the composite CVD outcome (HR: 0.55, 95% CI: 0.38–0.82, $P=0.002$) and a 44% reduction in all-cause mortality (HR: 0.56, 95% CI: 0.37–0.85, $P=0.005$).⁴⁴ The high CVD risk associated with diabetes and CKD stages 1 to 3 supports initiation of statin therapy when LDL is >100 mg/dl, with the achievement of an LDL goal of <70 mg/dl as a therapeutic option.

Initiation of statin treatment in patients with CKD stage 5 on hemodialysis (CKD 5D) treatment does not improve cardiovascular outcomes

More definite negative evidence in patients with CKD stage 5, at least in hemodialysis patients, comes from two randomized prospective placebo controlled trials, the German 4D (Die Deutsche Diabetes Dialyse) study in type-2 diabetes and the international AURORA trial.^{45,46} In 4D, 1255 hemodialysis patients in Germany with type-2 diabetes were randomized to receive atorvastatin 20 mg/day or placebo, whereas in AURORA therapy was rosuvastatin 10 mg daily versus placebo for 2766 international patients of which approximately one quarter had diabetes. Although both studies demonstrated just over 40% LDL reduction in the intervention groups, there was no significant difference in the cumulative incidence of the primary composite CVD endpoint over an average observation period of 4.0 years in 4D and 3.2 years in AURORA.

These data do not support initiation of a statin for dialysis patients without CVD. However, patients in whom statin therapy was initiated earlier in the course of CKD and those who develop cardiovascular indications should be treated with statin therapy.²⁹

Dyslipidemia may increase albuminuria and accelerate progression of diabetes and CKD

A number of observational studies report dyslipidemia to be associated with decreased kidney function in the general population and in patients with CKD, regardless of diabetes presence.²⁸ In the RENAAL Study, the unadjusted RR for the primary composite end point (doubling of serum Cr, end-stage renal disease, or death) among patients in the upper quartile of the distribution for total cholesterol and LDL was significantly higher than for those in the lower quartile.⁴⁷ Small short-term randomized studies report mixed results of the effect of statins on progression of diabetes in CKD. In patients with type 1 diabetes and microalbuminuria, simvastatin had no beneficial effect on either albuminuria or kidney function.⁴⁸ However, some randomized trials in type 2 diabetes reported beneficial effects of statins on albuminuria and kidney function relative to pre-treatment levels,^{49–52} but not relative to placebo or an alternative class of treatment for dyslipidemia.^{53,54} Whether dyslipidemia causes reduced kidney function, or results from reduced kidney

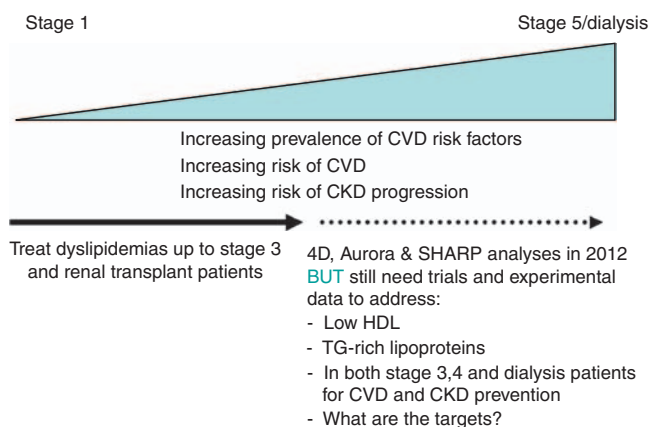


Figure 1 | Clinical equipoise on treating dyslipidemias in CKD.

function, or whether other conditions, such as proteinuria, cause both reduced kidney function and dyslipidemia cannot be determined from the available data, see Figure 1.

Statin myopathy

Statin myopathy encompasses a spectrum from relatively mild myalgias to more severe myositis and rare rhabdomyolysis.⁵⁵ Although myalgias may occur in up to 10% of patients, the important clinical relevance is self-discontinuation of statin therapy.⁵⁵ Current literature suggests that statins are generally safe in patients with impaired kidney function.^{28,29,43,44,56} However, treatment of kidney transplant recipients or glomerular disease patients concomitantly with calcineurin inhibitors and statins with similar P450 3A4 metabolism may increase risk of myopathy, particularly when combined with a fibrate.²⁸ Routine monitoring of liver and muscle enzymes is not supported by randomized trials in patients with CKD.^{29,56}

Other agents

Dose adjustments for fibric acid derivatives in CKD are recommended for fenofibrate, but not gemfibrozil.²⁸ The safety and efficacy of ezetimibe is supported by trial data in a patients with moderate CKD.⁵⁷ Bile acid sequestrants are safe for all levels of kidney function, but should be avoided for those with hypertriglyceridemia.

Limitations

There are no prospective randomized controlled trials available in diabetes and CKD stages 1 to 3. Recommendations made for patients are based on *post hoc* analysis with limited numbers of patients. The current recommendations need validation in people with diabetes and stage 4 CKD. The ongoing Study of Heart and Renal Protection, a randomized controlled trial of simvastatin 20 mg + ezetimibe 10 mg versus placebo daily in 6000 CKD and 3000 hemodialysis patients, may provide additional insights.⁵⁸ The discussion has primarily focused on LDL-lowering therapies (Figure 1), but in addition the potential pleotropic effects of statins, including their actions to attenuate oxidative stress, and improve endothelial function may also have a therapeutic

role. Case application is summarized in the Table 1. Data from the ACCORD lipid trial suggest that the routine addition of a fibrate to statin therapy for individuals with type-2 diabetes may not reduce the incidence of CVD events.⁵⁹ A recent consensus statement from the American College of Cardiology and ADA recommends measurement of a marker of the total burden of atherogenic particles, ApoB, and treatment to an ApoB, or a non-high-density cholesterol target for statin-treated patients at high risk, such as the patient described in the case.³⁵

IMPACT OF GLYCEMIC CONTROL ON VASCULAR INJURY IN CKD

Introduction

Patients with diabetes are well recognized to be at increased risk for CVD,^{60,61} particularly those with CKD.^{29,62} Clinical practice guidelines on management of hyperglycemia in CKD have been derived from investigations in type 1 and 2 diabetes in stages 1 and 2 (increased amounts of albuminuria/proteinuria with eGFR > 60 ml/min per 1.73 m²).²⁹ There is little clinical evidence derived from investigations of patients with eGFR < 60 ml/min per 1.73 m², or end-stage renal disease. Specifically, in CKD stages 3–5, there are only limited data from intervention studies regarding optimal HbA1c management. Further, there is minimal and controversial evidence addressing the impact of HbA1c reduction and CVD outcomes among patients with diabetes, in general.

Glycemic control and diabetes complications

Tight glycemic control in patients with both type 1 and type 2 diabetes reduces the risk of developing microvascular (CKD, retinopathy, neuropathy) complications, including incident microalbuminuria as well as macroalbuminuria based on randomized controlled trials such as the Diabetes Control and Complications Trial (DCCT/epidemiology of diabetes interventions and complications)⁶³ and the United Kingdom Prospective Diabetes Study (UKPDS)^{64,65} the Kumamoto Study⁶⁶ and the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study.⁶⁷ The microvascular data from ACCORD are yet to be published. These results support maintaining HbA1c concentrations as close to 7% as safely possible to prevent CKD characterized by albuminuria, consistent with guideline recommendations.^{3,29}

Only Observational studies suggest that tighter glycemic control is associated with a reduced risk of kidney disease progression or onset of end-stage renal disease.^{68–71} However, there is a lack of long-term trial data demonstrating that rate of progression can be influenced by tight glycemic control at later stages of CKD. Nevertheless, CKD progression is not the only criterion for keeping HbA1c levels near normal. Data supporting intensive glycemic control for preventing or decreasing other microvascular complications of diabetes, such as retinopathy, are strong.⁷²

The effect of tight glycemic control on macrovascular disease remains unclear, whether or not diabetes is complicated

by kidney disease. Data from the DCCT/EDIC Study suggest that risk of cardiovascular events is reduced with intensive insulin therapy and that this risk reduction is partly mediated by prevention of CKD.⁷³ Yet, other studies have not consistently shown a protective effect for tight glycemic control with regard to macrovascular complications. Recent data from the ACCORD study suggest that intensive glycemic control (HbA1c < 6.0%) to prevent CVD results in excess mortality in type 2 diabetic patients at high risk for heart disease,⁷⁴ although this was not corroborated by the similarly designed ADVANCE study.⁶⁷ Therefore, consensus guidelines recommend an HbA1c level < 7% to prevent CVD complications in the diabetes population with or without CKD.^{3,29}

Monitoring of glycemia in CKD

Individuals with CKD stages 1 and 2 have preserved kidney function and albuminuria. In these earlier stages, no changes from usual diabetes care are typically required for management of hyperglycemia or monitoring blood glucose. However, patients with eGFR < 60 ml/min per 1.73 m² often display comorbid complications contributing to advanced kidney disease including: poor BP control, mineral and bone disorders, malnutrition, and anemia due to decreases in erythropoietin production. In individuals with stages 3 to 5 CKD, these comorbidities contribute to impaired glucose metabolism and pharmacokinetics, which render these subjects at increased risk for hyperglycemia and hypoglycemia. Thus, it is imperative to monitor glycemia closely and adjust doses of medications appropriately to the level of eGFR. Although there are scant data regarding glucose monitoring in CKD, ADA guidelines should generally be followed.^{3,29}

Management of glycemia in CKD

The major risk in all diabetic patients to attain HbA1c < 7.0% is hypoglycemia, particularly for those treated with insulin, although the risk is lower in type 2 individuals.^{64,75} The UKPDS also showed that sulfonylureas are associated with a small risk of hypoglycemia.⁶⁴ The KDOQI guidelines for Diabetes and CKD provide extensive recommendations for dosing of drugs used to treat hyperglycemia in patients with CKD stages 3 to 5, and detailed management strategies are beyond the scope of this paper.²⁹

Nutrition in diabetic kidney disease

Obesity. Treatment of obesity in CKD should be directed at achieving weight loss, using exercise in the clinical context and a diet low in calories, fat, and sodium. In small observational studies, weight loss reduces proteinuria,^{76,77} and stabilizes progression of CKD.^{78–81} Recent evidence suggests that in morbidly obese subjects who fail to lose weight with traditional measures and develop complications of increased body mass index, bariatric surgery may be considered.^{74,75}

Protein intake

A dietary protein intake of 0.8 g/kg body weight (about 10–15% of total calories), the recommended daily allowance

for this macronutrient, is a level that has been targeted in nutritional intervention studies for stable outpatients with diabetes and stages 1 to 4 CKD.²⁹ Nutrition surveys indicate that most Americans eat in excess of the recommended daily allowance level.⁸² In two separate meta-analyses, low-protein diets reduced risks of progression of albuminuria/proteinuria and loss of GFR. The benefits were more pronounced in diabetics with CKD.^{83,84} More recently, even a modest limitation of dietary protein (0.89 g/kg body weight/day versus 1.02 g/kg body weight/day) reduced risk of CKD stage 5 or death (RR 0.23, 95% CI: 0.07–0.72, $P=0.04$) in persons with type 1 diabetes and stage 2 CKD.⁸⁵ Benefits of limiting dietary protein intake are more evident in type 1 than in type 2 diabetes, but fewer studies have been done in the latter population. Based on the available evidence, the KDOQI guidelines recommend limiting the dietary protein to the recommended daily allowance level of 0.8 g/kg body weight for CKD stages 1 to 4 to stabilize or reduce albuminuria, slow decline in GFR, and possibly prevent CKD progression.²⁹

At the other end of the spectrum, high-protein diets are a special concern in diabetes because they may increase albuminuria and accelerate loss of kidney function.²⁹ Higher protein intake appears to increase glomerular hyperfiltration and kidney damage in diabetes.^{86–89} Emerging epidemiologic evidence indicates that higher protein intake (≥ 20 versus 10% of total daily calories) is associated with loss of kidney function in women with mildly decreased GFR (CKD stages 1–2 inferred) and development of microalbuminuria in people with diabetes and hypertension.^{88,89} Therefore, diabetic persons with CKD should avoid high-protein diets ($\geq 20\%$ of total daily calories).²⁹

Sodium intake

The recommendation for daily sodium intake in the general population is 2400 mg, and even a more stringent < 1500 mg for nearly 70% of the US adult population, (African Americans, hypertension, or middle to advanced age).⁹⁰ Several randomized trials have demonstrated improvements in BP with dietary sodium restriction,^{91–94} with associated reductions in CVD end points.^{87,88} Patients with CKD are generally less able to excrete a sodium load, making the potential benefit even greater, although there are scant data.

Limitations

There are insufficient data to recommend any changes in guideline recommendations of HgbA1c $< 7.0\%$ in CKD at any stage. It is also important to recognize that management of diabetes will change based on the level of kidney function, especially at advanced stages of CKD (e.g., GFR < 60 ml/min per 1.73 m²), with particular attention paid to selection of medications regarding their side effects. Obesity is an emerging area of interest in the management of CKD and diabetes. Therapeutic lifestyle changes such as adjusting protein intake and weight reduction should be emphasized in the CKD population.

Case application

The case application in Table 1 shows glipizide 10 mg daily substitution for metformin in accordance with the Food and Drug Administration contraindication for serum creatinine 1.5 mg/dl or greater in men (1.4 or greater in women) for the risk of lactic acidosis.⁹⁵ This is not based on data but rather extrapolation from phenformin use. Some clinical studies have found this risk for lactic acidosis linked better to eGFR versus serum creatinine and suggest that risk increases at eGFR < 30 ml/min per 1.73 m².^{96,97} If there was a concern about the hypoglycemia risk with sulfonylureas, an alternative intervention is the use of short acting repaglinide 1 mg with meals instead of the biguanide. Additionally, other agents such as reduced doses of sitagliptin at doses adjusted for level of kidney function can be used in such patients in combination with other oral medications.

Group IV-heart failure: consequence of and influence on CKD

Most of the estimated five million heart failure patients in the United States are older adults,⁹⁸ with over one million hospitalizations and over 300,000 deaths due to heart failure annually occurring in patients who are 65 years and older. The average age of dialysis initiation is 68 years. Heart failure is the most common cause of death in stage 5 CKD and in many cases is prevalent before the initiation of dialysis. Currently, over half of the annual cost of heart failure care of an estimated 30 billion dollars is spent for inpatient care of heart failure.⁹⁸ Heart failure is commonly associated with coronary artery disease, hypertension, diabetes, and CKD. A study of 105,388 heart failure patients in the Acute Decompensated Heart Failure National Registry (ADHERE) reported that 57% of these patients had coronary artery disease.⁹⁹

Epidemiology of CKD in heart failure

Unlike the general population, the epidemiology of CKD in heart failure is not very well studied. Patients with high serum Cr levels are often excluded from randomized clinical trials in heart failure.¹⁰⁰ Data on the prevalence of CKD in heart failure are derived, therefore, at best, from large heart failure registries involving hospitalized acute heart failure patients. A study of acute hospitalized heart failure patients from the ADHERE registry of 75,382 (64%) patients with impaired kidney function, showed that 51,553 (44%), 15,553 (13%), and 8276 patients (7%), respectively, had stages 3, 4, or 5 CKD.¹⁰¹

Risk factors for CKD in heart failure

Prospective epidemiological data on risk factors for CKD are scarce, and most associations are derived from cross-sectional studies. Cross-sectional data from the NHANES survey suggest that in the general population, age, ethnicity, education, diabetes, hypertension, CVD, and body mass index are associated with CKD.^{102,103}

Data from the ADHERE registry indicate that age, sex, and ethnicity are associated with CKD.¹⁰¹ However, these associations were unique among stage 5 CKD patients, of whom about 68% were receiving chronic dialysis. Most heart failure patients with CKD were women (54, 58, and 54%, respectively, for stage 3, 4, and 5), whereas most with stage 1 and 2 kidney function were men (57 and 53%, respectively). The proportion of heart failure patients who are African Americans with stages 1 to 5 CKD were similar across all stages ranging from 39% in stage 1 to 33% in stage 5.¹⁰¹ This suggests that these patients were more likely to develop heart failure regardless of CKD stage. However, a separate analysis also showed that once CKD developed, African Americans were more likely to progress to stage 5 CKD, often requiring chronic dialysis.¹⁰⁴

In the Reasons for Geographic and Racial Differences in Stroke registry, the prevalence of stage 3 or higher CKD was higher among Whites (50 versus 34% for African Americans); however, the prevalence of stage 4 and 5 CKD was higher among African Americans (0.3 versus 0.1% for Whites).¹⁰⁵

In the ADHERE registry, however, the prevalence of systolic heart failure (ejection fraction <40%) was the lowest among patients with stage 5 CKD (45%, stage 5 versus 53%, stage 1).¹⁰¹ This suggests that either fewer patients with systolic heart failure progress to stage 5 CKD, or heart failure patients with low ejection fraction and stage 5 CKD receiving dialysis had disproportionately high mortality rates. This latter interpretation is supported by data from the United States Renal Data System, noting a 19% per annum mortality rate in dialysis patients, with heart failure as the most common etiology.¹⁰⁴

CKD as a risk factor for heart failure

Because heart failure and CKD share common risk factors and often coexist, it may be at times difficult to determine if CKD in heart failure is a case of prevalent or incident CKD, or a manifestation of the cardio-renal syndrome.^{106–110} Data from the Cardiovascular Health Study indicate that among older adults, increasing baseline serum creatinine was associated with a graded increase in the risk for incident heart failure.^{111,112} A further analysis of the Cardiovascular Health Study suggests that among older adults with no baseline CKD, presence of CKD identified by cystatin C level was associated with increased risk of heart failure.¹¹² CKD has a poor prognosis among African Americans; however, little is known about racial variations in the CKD-associated risk of heart failure.

In summary, CKD is associated with increased morbidity and mortality from heart failure. CKD is also associated with underuse of ACEi or ARB as part of a therapeutic regimen to achieve BP goals in these patients. Increases in serum Cr are common following administration of RAAS blockers in heart failure patients. The physiology of why this occurs is beyond the scope of this paper but the readers are referred to recent, in-depth reviews.^{107,108,113–115} Despite concerns of acute rises in serum Cr of up to 30%, use of these drugs has been

documented to improve cardiovascular and renal outcomes.^{2,15,16} Clinicians should routinely risk stratify heart failure patients by the presence of CKD based on eGFR values and take preventive and therapeutic measures based on current guidelines and appropriate nephrology consultation.

Approaches to further optimize this patient's cardiac function, reduce cardiovascular risk, and help normalize albuminuria would be the addition of an aldosterone antagonist such as spironolactone. Aldosterone antagonists are known to reduce mortality in heart failure patients.^{116,117} These agents are also known to reduce proteinuria, in an additive fashion when used with other RAAS blockers.²⁵ The concern about these agents is risk for hyperkalemia, however, recent studies show that the highest risk is among patients already on diuretics with RAAS and have a GFR <45 ml/min and serum potassium well above 4.5 mEq/l.²⁶ Table 1 summarizes changes implemented in this case based on the absence of these risk conditions.

DISCLOSURE

All the authors declared no competing interests.

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Influence of blood pressure targets on vascular injury in chronic kidney disease.

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WORK GROUP IV

The consequences and influence of heart failure on kidney function.

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