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Review Article

Diabetes Medication Management in Patients with Concurrent CKD

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Abstract

Patients with both diabetes and CKD (Chronic Kidney Disease) require a unique clinical approach to therapy. Chronic kidney disease carries an increased risk of morbidity and mortality, and drug dosing is often complicated due to reduced renal clearance and polypharmacy. Patients with diabetes are frequently prescribed multiple medications to reach glucose goals in addition to other therapies that reduce cardiovascular risk, such as aspirin, statins, and antihypertensive medications. Patients with CKD can also present with CKD-related complications like anemia and renal osteodystrophy, further adding to drug therapy. This review highlights the medication management of patients with diabetes that also have concurrent CKD, including the guideline recommendations, the importance of blood pressure and blood glucose goals, and unique challenges in drug selection. The review concludes with the importance of a multidisciplinary approach to the management for the patient with chronic kidney disease.

Introduction

Diabetes is the leading cause of CKD and the prevalence of diabetes in patients with CKD and the general population continues to increase [1,2]. In the United States, chronic kidney disease (CKD) remains the eighth leading cause of death. Individuals with CKD carry an increased risk of morbidity and mortality regardless of disease stage, and are at an increased risk of CKD-related complications that may affect quality of life [3]. Therefore, careful attention to glucose, along with other cardiovascular risk factors including blood pressure and cholesterol is essential. Caring for patients with CKD and diabetes can be complex and challenging due to polypharmacy and declining renal function. Maximizing therapeutic efficacy of medications, minimizing toxicities, and limiting disease progression is important. Due to the complex issues affecting this patient population, a clinical review was conducted to answer the questions regarding the most appropriate treatment goals for blood pressure and glucose, preferred drug therapy, and treatment of comorbidities. This review will discuss the findings from the literature review including treatment goals and selection of drug therapy in this unique population as well as the pivotal role of the interdisciplinary team.

General Treatment Approach

Hyperglycemia, over time, results in vascular target organ damage, including Diabetic Kidney Disease (DKD). The initial manifestation of DKD is persistent albuminurea in type 1 diabetes, and albuminurea is a marker for development of DKD in type 2 diabetes [4]. Intensive treatment of hyperglycemia prevents microalbuminuria and reduces progression to macroalbuminurea [5]. Glucose goals for patients with diabetes and CKD are the same for those with diabetes without CKD, and the majority of organizations including the American Diabetes Association (ADA), The National Kidney Disease: Kidney Disease Outcomes Quality Initiativve (KDOQI), and Kidney Disease: Improving Global Outcomes (KDIGO) recommend a hemoglobin A1c goal of <7% for most patients [4-6]. These organizations advocate a patient centered approach including adjustment in hemoglobin A1c goal for patient specific factors. Because many patients with CKD have multiple comorbidities and are predisposed to polypharmacy, a less stringent higher hemoglobin A1c goal may be justified [4]. Overall, glucose lowering is associated with delaying the onset and progression of urinary albumin excretion, estimated glomerular filtration rate (eGFR) decline, and the need for dialysis [4,5]. Although glucose lowering prevents progression of albuminuria, a cardiovascular risk factor, reduction in albuminuria through glucose lowering has not been directly linked to improved cardiovascular outcomes in clinical

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trials [5]. In addition to glucose lowering, guidelines suggest utilizing an Angiotensin Converting Enzyme(ACE)-inhibitor or Angiotensin Receptor Blocker (ARB) in normotensive patients with diabetes and albuminuria to prevent further kidney damage [4,5].

Tight Glycemic Control: Benefits vs. Risks

There is a significant amount of evidence supporting improved outcomes with a hemoglobin A1c goal of <7% [4], although some organizations including the American Association of Clinical Endocrinologists (AACE) recommend an optimal hemoglobin A1c goal of <6.5% due to additional benefits observed in some clinical trials [7]. However, achieving tight glycemic control may actually increase cardiovascular events and all-cause mortality in patients with CKD [8]. Severe hypoglycemia and death are also increased with declining kidney function [1]. An analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared outcomes between those with CKD (N=3,636) and those without (N=6,506). Risk for the primary outcome, the composite of the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, was significantly higher in patients with CKD (hazard ratio= 1.87; 95% CI: 1.651-2.11). Intensive glucose lowering (mean hemoglobin A1c=6.7%) in patients with CKD was associated with a 31% higher risk for all-cause mortality (P=0.01) when compared to standard glucose control (mean hemoglobin A1c=7.5%) [8]. This demonstrates the importance of individualizing hemoglobin A1c goals, which is an approach the ADA and AACE advocate [4,7].

Treating Comorbidities: Hypertension

Hypertension remains the second most common etiology of CKD, and CKD itself can lead to hypertension. Hypertension is also an important cardiovascular risk factor in patients with diabetes [9]. Patients with CKD generally have a more difficult time achieving blood pressure control and often need multiple agents to achieve blood pressure targets [6]. Historically, the blood pressure goal for all CKD patients was less than 130/80 mmHg [10]. The KDIGO and other organizations now support a general blood pressure goal of <140/90 mmHg [6,10,11]. Lower goals (<120 mmHg) have demonstrated benefits in CKD progression but have led to worsening CVD outcomes. However, KDIGO continues to recommend a goal of <130/80 mmHg in patients with albuminurea based upon improved kidney outcomes in this population [6].

Preferred agents for treating hypertension in patients with CKD and albuminuria include ACE-inhibitors and ARB's. These agents interfere with the Renin-Angiotensin-Aldosterone System (RAAS) leading to vasodilation of the efferent glomerular arterioles, decreased intraglomerular pressure and reduction in urine albumin excretion [6]. They are also the preferred first line agent according to the ADA and AACE guidelines [6]. When using ACE-inhibitors or ARB's, it is important to monitor serum creatinine and potassium [11]. Serum creatinine is often increased on initiation, due to reduced pressure in the renal arterioles, and up to a 30% increase is considered clinically acceptable. Additionally, ACE-inhibitors and ARB's should be avoided in individuals with bilateral renal artery stenosis and used cautiously in patients with fluid depletion [6].

Patients with CKD often require two or more agents to control hypertension [6,11]. ACE-inhibitors and ARB's should not be used concurrently, but can be combined safely and effectively with other first line antihypertensive agents including diuretics and calcium channel blockers to optimize the treatment of hypertension. Clinicians must be cognizant however, that thiazide diuretics lose effectiveness in CKD stages 4 and 5, in which case a loop diuretic is preferred [6]. ACE-inhibitors and ARB's can also be combined with beta blockers, especially in patients who have strong indications for their use, such as heart failure [11].

Diabetes Medication Selection

According to the ADA and AACE guidelines, the first line agent for glucose lowering in patients with type 2 diabetes is metformin due to its proven safety and efficacy [4,7]. However, the U.S. Food and Drug Administration (FDA) advises that metformin not be used when serum creatinine is over 1.4 mg/dL in women and 1.5 mg/dL in men, as there is a theoretical risk of lactic acidosis in a functionally compromised kidney. In reality, rates of lactic acidosis appear to be extremely low with metformin [1]. Therefore, other countries have adopted less stringent thresholds based on eGFR. The KDIGO guidelines suggest reducing metformin dose when eGFR<45 ml/min to 1000 mg/day and discontinuing when eGFR<30 ml/min to allow greater use of this highly effective glucose-lowering agent [1].

Other glucose lowering agents may predispose patients to hypoglycemia since their action is prolonged with reduced kidney function. This especially includes sulfonylureas and meglitinides. If a sulfonylurea is used, glipizide is preferred secondary to its short half-life and lack of active metabolites; other sulfonylureas should not be utilized in moderate kidney disease. Thiazolidinediones are metabolized by the liver, and can be used safely in CKD, although patients need to be cautious because of possible fluid retention. The dipeptidyl peptididase-4 (DPP-4) inhibitors, glucagon-like pepetide-1 (GLP-1) receptor agonists, and alpha glucosidase inhibitors are other second line agents that can be used, but many have renal thresholds requiring dose reductions or cessation beyond a certain eGFR [5]. The newest drug class to treat type 2 diabetes is sodium-glucose co-transporter 2 (SGLT2) inhibitors. Due to their mechanism of action in working on the proximal renal tubule to prevent renal sodium and glucose reabsorption, the agents in this class have renal thresholds where they should not be used including an eGFR<45 ml/min (canagliflozin) or eGFR<60 ml/min. (dapagliflozin, empagliflozin) [12]. For patients with severe CKD, insulin may be the safest choice. Although there are technically no dose adjustments recommended for insulin in patients with CKD, there is a higher risk of hypoglycemia due to reduced renal clearance; as a result, all CKD patients with diabetes require careful monitoring of blood glucose with gradual dose titration [4,5].

Utilizing an Interprofessional Colloborative Approach to Patient Care

Patents with CKD and diabetes represent a unique population that require a focused multi-disciplinary approach to ensure safe use of medications and prevention of disease progression. In addition to the physician, other healthcare professionals such as pharmacists, dieticians, social workers, psychologists, and

nurses have pivotal roles in patient management. Because of the complex needs in maintaining existing kidney function, limiting progression of disease through the management of comorbidities, and treatment of CKD-related complications, CKD patients are often exposed to polypharmacy. Pharmacists represent a health-care discipline with the knowledge and expertise to contribute to the multidisciplinary team by performing prospective drug utilization review, delivering patient education, and providing counseling on lifestyle modifications. For patients who progress to dialysis, the pharmacist has a pivotal role in assisting in the appropriate delivery of medications that require specific dialyzing considerations. If possible, the patient should always be included on the decision to continue or discontinue a medication based on risks and benefits [13]. Dieticians are well versed in the implementation and maintenandce of dietary lifestyles that are appropriate for the kidney patient. Malnutirtion is often a problem in CKD patients, and therefore nutritionists and dieticians can be utilized to ensure that patients are maintaining appropriate diets in accordance with kidney rescritions [14]. Finally, because living with chronic kidney disease can be overwhelming for the patient physically, emotionally, and psychologically, social workers and psychologists can be utilized to ensure that patients possess appropriate coping and problem solving sklls for lifestyle management

Conclusion

Diabetes and CKD are on the rise in the population. Glucose lowering is important to prevent microvascular and macrovascular complications. Patients with both diabetes and CKD require a unique clinical approach. Although there are clinical guidelines to help clinicians manage CKD and its related complications and comorbidities, there are many clinical challenges surrounding optimal treatment such as the preference in type of drug therapy and blood glucose and blood pressure goals Therefore, clinical judgment is very important. An interdisciplinary team equipped with the knowledge and tools to ensure the most optimal well-rounded care is essential in helping patients to meet their goals.

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