Management of Chronic Kidney Disease and End-Stage Renal Disease in Diabetes

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ABSTRACT

Diabetic nephropathy occurs in 20–40 % of patients with diabetes mellitus and is the leading cause of End-Stage Renal Disease (ESRD) in North America. This review outlines the evidence-based approach to the management of progressive Chronic Kidney Disease (CKD) and ESRD in diabetes with the objective of guiding future physicians. In addition to patient education on diabetes management, vigilant annual screening for microalbuminuria and increased serum creatinine is the first step towards ensuring early treatment of CKD, well before the onset of frank proteinuria. In addition to controlling hyperglycemia, issues of hypertension and dyslipidemia should be addressed to prevent onset and progression of CKD, with Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers being the drugs of choice for controlling hypertension in these patients and statins being the pharmacological mainstay for dyslipidemia. Furthermore, clinicians must address the consequences of CKD, particularly anemia, hyperphosphatemia, and vitamin D deficiency. Lifestyle modifications such as a low protein diet, smoking cessation, and cardiovascular and resistance exercises could help prevent progression and morbidity in CKD. When patients progress to irreversible kidney failure or ESRD, early (pre-emptive) transplantation before the initiation of dialysis has been shown to maximize survival. Owing to lower risk and better preservation of residual kidney function, peritoneal dialysis is now recommended as the initial modality of dialysis in most ESRD patients in the absence of a kidney transplant. Ultimately, effective management of kidney disease in diabetes relies on the collaborative efforts of the patient, their support system, and their multi-disciplinary healthcare team.

KEYWORDS: *diabetes mellitus, diabetes complications, diabetic nephropathy, kidney diseases, kidney failure, chronic*

INTRODUCTION

Diabetes mellitus, a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion and/or defective insulin action, has become a worldwide pandemic affecting over 285 million people.[1,2] With devastating complications in the absence of effective management, it is vital that patients with diabetes be managed in a consistent and evidence-based manner.[3]

Of all the microvascular complications of diabetes, chronic kidney disease (CKD) is especially concerning owing to its debilitating nature.[4] Specifically, diabetic nephropathy occurs in 20–40 % of patients with diabetes mellitus and is the leading cause of end-stage renal disease (ESRD) in North America.[5,6]

While clinical guidelines for the care of patients with progressive CKD and ESRD have been developed with good consensus in the nephrology community, existing data indicates that much work remains to achieve acceptable levels of recommended care in these patients.[7]

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MANAGEMENT OF CHRONIC KIDNEY DISEASE

CKD is clinically defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2 body surface area, with or without evidence of kidney damage, for 3 months or longer.[8] The conventional method to keep track of the various aspects of CKD management in diabetes involves using the GFR to differentiate between the different stages of CKD as each successive stage necessitates further steps in management additional to those at the previous stage.[5]

Screening

The assessment of microalbuminuria (defined as an elevated albumin excretion rate in the range of 30–300 mg/24h) and an elevated urine albumin-creatinine ratio (ACR) ratio (defined as > 2.0 mg/mmol in males or > 2.8 mg/mmol in females) are both important indicators of diabetic nephropathy as it is an early clinical manifestation that presents several years before changes in GFR.[2,5,9] Overexcretion of albumin typically increases at a rate of 15 % per year, eventually culminating in macroalbuminuria (> 300 mg/24h).[10] The distinction between microalbuminuria and macroalbuminuria is significant: while non-proteinuric CKD

patients are at high cardiovascular risk, they have a much slower progression to ESRD.[11] Macroalbuminuria, on the other hand, is a strong risk factor for progression from CKD to ESRD.[9,11–12]

The American Diabetes Association recommends that both microalbuminuria and serum creatinine levels be assessed annually in patients with diabetes to screen for diabetic nephropathy.[12] Risk profiles in persons with diabetes are also important, as genetic influence (positive family history and ethnicity) is considered the most important factor for diabetic nephropathy.[6,13]

Hyperglycemia

Guidelines continue to recommend a target Hemoglobin A1c (HbA1c) level < 7 %, though there is little evidence that this improves outcomes.[14–16] Although the mechanism is not fully understood, a positive correlation exists between elevated HbA1c and the development and progression of microalbuminuria.[14–16] For instance, in the six years following the landmark Diabetes Control and Complications Trial, 4.5 % of the intensive treatment group with an average HbA1c of 7.2 % developed microalbuminuria compared to 12.3 % of the conventional treatment group with an average HbA1c of 9.1 %.[17]

Hypertension

Persons with diabetes and insufficient blood pressure control are at a high risk for both developing cardiovascular disease and progressing further with their nephropathy.[4] Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are the drugs of choice for controlling hypertension in patients with diabetes and albuminuria, but additional antihypertensive drugs should be prescribed if blood pressure remains over 130/80 mmHg despite lifestyle interventions and the use of an ACEI/ARB.[18–21]

It is currently recommended that adults with diabetes and persistent albuminuria receive an ACEI/ARB to delay progression of CKD, even in the absence of hypertension.[22–24] Thiazide-like diuretics should also be considered, with the addition of furosemide (Lasix®) for those who fail monotherapy.[2]

Despite current consensus in management, less than 20 % of patients with CKD actually meet their blood pressure goals.[25] The use of selective endothelin A receptor antagonists (potent vasodilators) for the treatment of resistant hypertension in CKD has been recently examined in clinical trials, proving effective in reducing blood pressure and improving proteinuria.[26–28] However, their use is currently limited by a significant side effect profile including increased sodium retention.[26]

Dyslipidemia

Continual screening and correction for dyslipidemia are major requirements in management of diabetic nephropathy, aiming for a low-density lipoprotein (LDL) level of < 2.59 mmol/L.[5] Statins are the preferred drug for lowering LDL levels and have been found to lower the incidence of cardiovascular events in this population.[14,28] If the patient also has a triglyceride level > 5.64 mmol/L, then fibrates are the recommended medication, although the dosage must be reduced appropriately to accommodate the decreased renal function.[28] It is important to note the increased risk of adverse effects such as rhabdomyolysis when both statins and fibrates are used in patients with GFR < 30 mL/min/1.73m^2, more so with gemfibrozil than fenofibrate.[29,30] When these drugs are used together, it is prudent to limit the statin dosage and monitor creatine kinase concentrations to identify individuals with myositis.[30]

Vitamin D Deficiency and Hyperphosphatemia

Reduced GFR leads to reduced renal excretion of phosphate, which in turn activates the release of parathyroid hormone from the parathyroid glands in addition to inhibiting activated vitamin D synthesis.[28,31] Consequences of hyperphosphatemia include deficiency of active vitamin D and secondary hyperparathyroidism with associated calcium disturbances. These are linked to abnormalities in bone homeostasis (known as renal osteodystrophy), vascular and soft tissue calcification, increased cardiovascular events, and death.[32–34]

The first treatment of choice for managing abnormalities in mineral metabolism is dietary restriction of phosphorus, although judicious use of phosphate binders and activated vitamin D can also be used to alleviate hyperphosphatemia.[28,35]

Anemia

Although the prevalence of anemia is much higher among patients with a GFR < 30 mL/min/1.73m^2, its treatment in CKD is a topic of much controversy and ongoing research.[36] As per the Kidney Disease Outcomes Quality Initiative guidelines, the goal for hemoglobin levels is 100–120 g/L, and it is recommended that patients be treated with erythropoiesis-stimulating agents (ESAs) if hemoglobin is found to be less than 100 g/L.[2,28,37] However, there is evidence suggesting that such aggressive treatment of anemia may increase CKD progression.[37,38] For instance, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial investigators found that more patients assigned to complete correction of anemia versus partial correction progressed to dialysis at the end of the study.[39]

Additionally, as many as 45 % of patients with CKD have been shown to be iron deficient.[40] Treatment involves small repeat doses of intravenous iron, which have been shown to be more effective than infrequent, large doses for maintaining levels of hemoglobin and reducing the need for ESAs.[41]

Lifestyle Modifications

Loss of renal function is also prevented by lifestyle factors: low protein diets and discontinuation of smoking have been shown to delay the progression of diabetic nephropathy.[42] Additional evidence in support of smoking cessation in persons with diabetes comes from a recent study showing reduced development of macroalbuminuria.[43]

Decreased physical activity has also been associated with an increase in mortality, particularly among patients on dialysis.[44] Exercise training not only improves physical performance-based measures but also decreases the risk of cardiovascular disease, increases protein uptake into skeletal muscles, and improves dialysis efficiency.[45] While androgens and growth hormone have been shown to improve lean body mass and strength, longer-term studies of safety and efficacy are needed before recommending their use in ESRD patients.[45]

MANAGEMENT OF END STAGE RENAL DISEASE

ESRD, a continuum of CKD, is defined as irreversible kidney failure treated with dialysis or transplantation.[46] Active participation from the patient and family is required for successful treatment of ESRD as involvement has been shown to promote non-emergent initiation of dialysis, lower morbidity and improved rehabilitation, less frequent and shorter hospital stays, and improved survival.[47]

Kidney Transplantation

A large body of literature attests to the survival benefits of patients undergoing kidney transplantation compared to those remaining on dialysis.[48] Several recent studies have demonstrated significantly improved patient and allograft survival as well as lower rates of delayed graft function or acute rejection episodes in those with preemptive transplants versus those who were on dialysis for a period of time before transplantation.[49] Recent evidence also suggests that simultaneous pancreasckidney transplantation is highly superior to kidney transplantation alone, with survival benefit already visible after five years of follow-up.[50] However, it has been hypothesized that intensified glycemic control (HbA1c < 6.5 %) may be the true differentiating factor for survival in patients with diabetes undergoing either combined or kidney only transplantation, although adverse events including hypoglycemia have been reported with the achievement of such difficult targets.[51]

Hemodialysis

Hemodialysis is found in two variants in which the primary mechanism of both is solute removal via diffusion: conventional hemodialysis, where patients receive hemodialysis in a clinic three times a week for 4 hours/session, and nocturnal hemodialysis, where patients are trained to do their own hemodialysis while they sleep, 5–6 nights/week.[52] Hemodialysis is a relatively safe procedure, but there are several complications that can occur including hypotension, cardiac arrhythmias, muscle cramps, anaphylaxis, and Restless Leg Syndrome.[52] However, with proper monitoring and prompt treatment, many of these complications can be avoided. Of note, better glycemic control (HbA1c < 7.5 %) has been shown to predict better survival of diabetic ESRD patients starting hemodialysis treatment.[53]

Peritoneal Dialysis

Compared to hemodialysis, peritoneal dialysis offers lower risk of death across all subgroups for the first 1–2 years of dialysis and is now recommended for use as the initial modality of dialysis in the majority of ESRD patients due to the lower prevalence of infections and better preservation of residual renal function.[54] The two common choices for peritoneal dialysis are Continuous Ambulatory Peritoneal Dialysis and Automated Continuous Cycling Peritoneal Dialysis, both of which function by infusing peritoneal dialysis fluid in the peritoneal cavity and draining it 4–6 hours later with the number of exchanges varying according to patient size, peritoneal membrane permeability, and residual kidney function.[52]

Benefits of using peritoneal dialysis include that of self-discipline for the patient, a sense of ownership and responsibility for disease and self-management, and lower morbidity and mortality.[52] An important caveat here for the diabetic patient is to avoid using high-glucose peritoneal dialysis solution, as this has been associated with worsening diabetes mellitus, lower serum albumin, and lower residual renal function.[54,55] The most common complication with peritoneal dialysis is peritonitis, which can be treated empirically with intraperitoneal antibiotics.[52]

CONCLUSION

Kidney disease is a serious complication of diabetes that requires intensive management and treatment. While the ultimate goals of renal therapy in patients with diabetes and kidney disease include prevention of progression to ESRD, reversal of uremic symptoms, and maximization of quality of life, this cannot be accomplished without the cooperation and active participation of the patient, their support system, and members of the healthcare team.

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