Approach to the Patient with Type 2 Diabetes and Progressive Kidney Disease

Elizabeth R. Seaquist and Hassan N. Ibrahim

Divisions of Endocrinology and Diabetes (E.R.S.) and Renal Diseases and Hypertension (H.N.I.), Department of Medicine, University of Minnesota, Minneapolis, Minnesota 55455

Type 2 diabetes is the leading cause of end-stage kidney disease in the United States. The management of patients with type 2 diabetes and progressive kidney disease requires a comprehensive approach that includes aggressive blood pressure control with agents that also lower urinary protein excretion and optimization of glucose and lipid control while remaining cognizant of the therapeutic limitations imparted by renal dysfunction. Clinicians must also address the co-morbidities associated with renal failure such as anemia and secondary hyperparathyroidism. Diabetic nephropathy typically follows a slowly progressive course from albuminuria to azotemia. Consequently, optimal care includes planning for the management of impending renal failure long before the patient requires dialysis or transplantation. (J Clin Endocrinol Metab 95: 3103–3110, 2010)

A 68-yr-old woman has been followed in our clinic for more than 15 yr. She was diagnosed with type 2 diabetes, hyperlipidemia, and hypertension at the age of 47. She was initially treated with metformin, atorvastatin, and hydrochlorothiazide and maintained hemoglobin A1c below 7.0%, low-density lipoprotein (LDL) cholesterol below 100 mg/dl, and blood pressure below 135/80 for many years. At age 59, she was noted to have an increase in her urine albumin to 54 mg/g of creatinine, and lisinopril was added to her regimen. Three years later at age 62, her serum creatinine increased to 1.56 mg/dl, and her glomerular filtration rate (GFR) was estimated to be 36 ml/min. Her hemoglobin A1c increased to 7.2%, and she began to experience paresthesias in her feet. The metformin was discontinued, and she was started on glargine insulin. At age 63, she developed proliferative retinopathy in her right eye and underwent laser photoocoagulation. Bilateral macular edema developed at age 65.

At a recent visit, she reported compliance with her medications that included lisinopril, hydrochlorothiazide, diltiazem, glargine, atorvastatin, and aspirin. She checked her blood sugars at home two to four times each day and...
found them to range from 100–250 mg/dl. She continued to walk 30 min each day. She still experienced paresthesias in her feet at night, but her sleep was not disturbed by these symptoms. Her body mass index was 38.2 kg/m². Her blood pressure was 142/90 mm Hg, and heart rate was 68 bpm. Her retinal exam was significant for panretinal photocoagulation changes with scattered dot hemorrhages and macular edema in both eyes. Heart, lung, and abdominal exams were unremarkable. Pulses in her feet were reduced, but her feet were warm and without ulcers. She was unable to detect a Semmes-Weinstein 5.07 monofila-
ment on the soles of her feet. Her hemoglobin A1c was 7.9%, serum creatinine was 2.45 mg/dl, GFR was estimated to be 20 ml/min, calcium was 9.8 mg/dl, phosphorus was 4.6 mg/dl, PTH was 75 pg/ml (normal, 12–72), total cholesterol was 188 mg/dl, triglycerides were 82 mg/ dl, high-density lipoprotein cholesterol was 42 mg/dl, LDL cholesterol was 131 mg/dl, and hemoglobin A1c was 10.8 g/dl.

Background

Type 2 diabetes is the leading cause of end-stage kidney disease in the United States (1), and as the epidemic of diabetes continues, endocrinologists will face an increasing number of such patients in their practice. Evidence now demonstrates that management in the early stages of diabetes has a significant impact on who develops chronic kidney disease and how quickly it develops. Studies have conclusively shown that glycemic control matters; the incidence of diabetic nephropathy is consistently reduced in subjects with diabetes randomized to intensive glycemic control (A1c ~7% or lower) compared with their respective standard control groups (2–4). The management of hypertension and hyperlipidemia has also been shown to have an impact on the rates at which diabetic nephropathy develops. However, diabetic nephropathy can develop even in patients who achieve target levels for glycemia, blood pressure, and lipids. The management of these patients over the course of their disease becomes increasingly more complex (Table 1), as is illustrated in the case. In this article, we will discuss our approach to the care of patients with type 2 diabetes and progressive kidney disease.

The Natural History of Diabetic Nephropathy

From patients with type 1 diabetes, we know that diabetic nephropathy only develops after a decade or more of exposure to diabetes. However, because the date of onset of type 2 diabetes is nearly always uncertain, it is not un-
common to find patients with abnormal kidney function at the time of diabetes diagnosis. Not all patients with diabetes are destined to develop diabetic nephropathy. Evidence from the United Kingdom Prospective Diabetes Study suggests that less than 30% of patients with diabetes will develop renal impairment over 15 yr of follow-up (5). Diabetic nephropathy is believed to be a progressive disease characterized first by the appearance of microalbuminuria followed by the progression to macroalbuminuria, rising serum creatinine, hypertension, and ultimately to kidney failure (Fig. 1) (4, 6). However, more recent data suggest that many patients with type 2 diabetes will not display microalbuminuria before experiencing a decline in their renal function (5). The progression to end-stage renal diseases usually occurs over years, although not all patients follow this course. The diagnosis of diabetic nephropathy can be made in a patient with diabetes by the persistent presence of albumin in the urine, or an unrelenting rise in serum creatinine, or a reduction in GFR. Patients with more advanced disease will frequently have evidence of other diabetic complications. If the clinical picture is compatible with this course, a kidney biopsy is rarely needed for diagnosis. However, in diabetic patients with rapidly progressive kidney failure or evidence of an active urinary sediment, other diagnoses should be considered.

Management Strategies

Glycemic control

Maintaining good glycemic control is important in patients with progressive renal disease. Several studies have demonstrated that the rate at which kidney disease develops can be slowed by good glycemic control (7, 8). In addition, good glycemic control will reduce the risk of developing diabetic retinopathy and neuropathy. The benefits of good glycemic control on cardiovascular disease in patients with advanced diabetic nephropathy has not been studied in a randomized clinical trial, but recent results of studies done in patients with type 2 diabetes and relatively normal kidney function suggest that there is little benefit (2, 9), and perhaps some harm (10), with respect to cardiovascular events and mortality in reducing the hemoglobin A1c to less than 7%. As a result of these investigations, we recommend that a hemoglobin A1c target of 7.0% is appropriate for the majority of patients with diabetic nephropathy. A lower target will increase their risk of hypoglycemia and may increase their risk of mortality, whereas a higher target may accelerate the rate at which renal failure and other diabetes complications develop. The selection of the optimal hemoglobin A1c needs to be
personalized for each patient by considering the relative risks and benefits of different levels of glycemia.

With advancing kidney disease, the pharmacological options for glycemic management are reduced (Table 2). Metformin carries a black box warning that lactic acidosis may develop in patients with kidney disease who take this drug, although this has been difficult to prove in careful evaluation of large populations of patients exposed to the drug (11, 12). Nonetheless, most practitioners will stop the drug when serum creatinine rises above the normal range. Drugs that rely on renal excretion will accumulate in the setting of kidney disease, thereby causing serious

### TABLE 1. Management of diabetic nephropathy by stage of renal function

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min per 1.73 m² body surface area)</th>
<th>Management recommendations</th>
<th>Drug regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or mildly increased GFR</td>
<td>≥90</td>
<td>A1c goal ~ 7.0% BP goal &lt;130/85 LDL goal &lt;100 mg/dl</td>
<td>Add ACE/ARB if urine microalbumin ≥30 mg/g creatinine</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60–89</td>
<td>A1c goal ~ 7.0% BP goal &lt;130/85 LDL goal &lt;100 mg/dl</td>
<td>ACE/ARB recommended for all patients</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
<td>A1c goal ~ 7.0% BP goal &lt;130/85 LDL goal &lt;100 mg/dl</td>
<td>ACE/ARB recommended for all patients</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
<td>A1c goal ~ 7.0% BP goal &lt;130/85 LDL goal &lt;100 mg/dl</td>
<td>Insulin therapy recommended for most patients with diabetes</td>
</tr>
<tr>
<td>5</td>
<td>End-stage renal failure</td>
<td>&lt;15 or dialysis</td>
<td>Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH &gt;2 × upper limits of normal</td>
<td>Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH &gt;2 × upper limits of normal</td>
</tr>
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BP, Blood pressure; ACE, angiotension-converting enzyme inhibitors; Hgb, hemoglobin.
consequences for the patients. Most sulfonylurea drugs are cleared at least in part by the kidney and can cause unexpected hypoglycemia in patients with kidney disease (13). Glipizide is the exception in this drug class because it is metabolized into inactive metabolites by the liver that are then excreted in the urine. Therefore, this drug can be safely used in patients with progressive kidney disease. The meglitinides are agents similar to sulfonylureas that work by enhancing insulin secretion. Nateglinide is metabolized to active metabolites and should be avoided in patients with kidney disease because of the risk for hypoglycemia. Repaglinide does not carry this risk because it is metabolized by the liver. α-Glucosidase inhibitors such as acarbose or miglitol also accumulate in kidney disease and increase the risk of hypoglycemia. Use of these drugs is not recommended in patients with renal disease. The half-life of exenatide increases as a function of renal function, and can be modified by careful management of glycemia, hypertension, and hyperlipidemia. ESRD, End-stage kidney disease. Adapted from Refs. 4 and 6.

**TABLE 2.** Safety of diabetes-related drugs in renal dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose must be modified in renal failure</th>
<th>Contraindicated in renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>Sitagliptin</td>
<td>Metformin</td>
</tr>
<tr>
<td>Thiazolidenediones (rosiglitazone, pioglitazone)</td>
<td>Glyburide, glimepiride</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td></td>
<td>Nataglinide α-Glucosidase inhibitors (acarbose, miglitol)</td>
</tr>
</tbody>
</table>

![Image](3106.png)

**FIG. 1.** Typical progression of diabetic kidney disease. Exposure to diabetes is required for diabetic nephropathy to develop in susceptible patients. The time at which the complication becomes clinically apparent and the rate at which it progresses is variable and can be modified by careful management of glycemia, hypertension, and hyperlipidemia. ESRD, End-stage kidney disease. Adapted from Refs. 4 and 6.

inhibitors like sitagliptin can be used in advanced kidney disease, but the dose should be reduced by 50% for patients with GFRs between 30 and 50 ml/min and by 75% for patients with GFRs less than 30 ml/min (15). Thiazolidenediones like rosiglitazone and pioglitazone are hepatically cleared and consequently will not accumulate in patients with kidney disease (13). Both drugs, however, are associated with heart failure and edema and are better avoided in patients with advanced kidney disease.

Because so many drugs need to be avoided in patients with kidney disease, many practitioners prefer to manage glycemia exclusively or at least in part with insulin. Although insulin clearance is reduced by renal dysfunction, thereby increasing the risk for hypoglycemia, the doses can be easily reduced as needed. The development of regimens of insulin replacement that mimic physiological insulin secretion where long-acting analogs like glargine or detemir are used as basal insulin and short-acting analogs like aspart, lispro, or glulisine are used as bolus insulin may help patients achieve target glycemia without experiencing as many episodes of hypoglycemia. Although few studies have examined the pharmacokinetics of insulin analogs in patients with advanced kidney disease, the actions of these insulins appears to be the same as in patients with normal kidney function (16).

**Blood pressure management**

Successful treatment of hypertension is critically important in patients with kidney disease and likely slows the rate of progression. The great benefit from blood pressure reduction can be easily demonstrated by considering the rate of GFR decline at different levels of systolic blood pressure. A diabetic subject with a GFR of 50 ml/min and a systolic blood pressure above 160 mm Hg will, on average, lose 12–14 ml/min/yr and therefore will require renal replacement therapy in 4–5 yr. In marked contrast, a diabetic patient with a similar level of GFR but with a systolic blood pressure below 130 mm Hg will only lose 2–5 ml/min/yr and may not require renal replacement therapy for 10–20 yr (17). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are currently considered the cornerstone for the treatment of hypertension in the setting of both diabetic and nondiabetic kidney disease. Their potent hypotensive effects, favorable cardiovascular properties, and ability to reduce proteinuria have been responsible for their popular use. Unfortunately, akin to tight glycemic control, using ACEIs or ARBs even at maximal dose fails to eradicate proteinuria, and many diabetic subjects progress to end-stage kidney disease. Although proteinuria is generally
considered a marker of kidney disease, there is compelling evidence that high levels of albuminuria may actually hasten disease progression. Therefore, additional strategies have been tested in diabetic subjects in whom proteinuria does not improve despite ACEIs or ARBs and tight blood pressure control. Combining the two agents has been studied in small trials that mainly employed a crossover design (18); an additional reduction in proteinuria has been noted in some but not in others and therefore, cannot be recommended at this time, particularly in view of the adverse cardiovascular events noted with combination therapy in the TARGET Trial (19). Adding an aldosterone antagonist to ACEI or ARBs has also been studied and should be considered in the heavily proteinuric diabetic patients. Extreme caution should be exercised when using any of the above-mentioned agents because they may predispose to the development of hyperkalemia, a particularly important issue in diabetics who are at high risk of developing hyporeninemic hypoaldosteronism. Most recently, the renin blocker aliskerin has been compared with placebo on the background of ARB treatment in type 2 diabetics with nephropathy and, at least in the short term, does offer additional antiproteinuric benefit (20). For the diabetic patient who is intolerant to drugs that interrupt the renin-angiotensin aldosterone system, the use of non-dihydropyridine calcium channel blocker in conjunction with a diuretic should be the next strategy. In all, however, achieving a systolic blood pressure below 130 mm Hg should be the number one priority, rather than the class used to treat hypertension.

Lipid management

Hyperlipidemia is very common in type 2 diabetes and is known to increase the risk of cardiovascular disease. The risk of having a fatal myocardial infarction is as high in a person with diabetes as it is in a person without diabetes who has already had a heart attack (21), and multiple studies have demonstrated that reduction of LDL cholesterol in patients with diabetes using statins will reduce this risk (22, 23). Therefore, all patients with diabetes should be treated with a statin unless their LDL cholesterol is already less than 100 mg/dl or a contraindication is present. Hyperlipidemia is also associated with an increase in the rate of progression of the diabetic nephropathy (24), and treatment with a statin has also been shown, in post hoc analyses of large randomized trials, to reduce this rate but has not been studied in a prospective rigorous manner (25). Interestingly, statin therapy does not appear to reduce cardiovascular disease in patients with end-stage kidney disease but does benefit patients with less severe renal disease (26).

Management of Comorbidities Related to Progressive Renal Disease

Anemia

An appreciable decline in the renal production of erythropoietin occurs when the GFR reaches 50–60 ml/min, and anemia is universal by the time patients reach end-stage kidney disease. The introduction of erythropoietin has revolutionized anemia management in chronic kidney disease in the sense that it has reduced the frequency of blood transfusions and resulted in improvement in quality of life. Traditionally, this injectable hormone is given when the hemoglobin level drops below 11 g/dl and concomitantly with iron supplementation (27). Recently, however, the largest randomized placebo-controlled trial in subjects with type 2 diabetes and GFR of 30–60 ml/min not only challenged this threshold for erythropoietin use but also raised concerns about its safety. In this trial, subjects randomized to placebo (hemoglobin target of 9 g/dl) did as well as those assigned to a hemoglobin of 13 g/dl in terms of all-cause mortality (28). However, the high hemoglobin levels were associated with a 92% increase in the risk of stroke. At this point, therefore, this drug should be reserved until the hemoglobin level reaches 9 rather than 11 g/dl and patients are fully informed about the risk of stroke.

Secondary hyperparathyroidism

As GFR declines, a state of secondary hyperparathyroidism ensues. The latter is driven by the relative hypocalcemia that stems from the retention of phosphorous and decreased production of 1-α hydroxylase. To combat hyperphosphatemia, the production of fibroblast growth factor-23 increases. There are now multiple pieces of evidence suggesting that fibroblast growth factor-23 is associated with an increase in cardiovascular mortality in both diabetic and nondiabetic patients (29). At the present time, restricting phosphorus intake as GFR declines and the use of phosphate binders are the main strategies to deal with this issue. Unfortunately, most of these are calcium based and should probably be avoided in diabetic patients who are prone to vascular calcifications. Sevelamer-based products, a resin that binds phosphorus in the gut and is not calcium based, is preferable. In addition, starting an active form of vitamin D when the PTH is 3- to 5-fold higher than normal is currently recommended. Despite these approaches, diabetic nephropathy patients continue to experience higher risks of fractures and also adynamic bone disease.

Preparing for impending end-stage kidney disease

Even with the best medical management, the majority of patients with diabetic nephropathy will proceed to end-
stage kidney disease. Fortunately, most patients are identified sufficiently early in their course to make plans for how they would like their end-stage kidney disease treated. In general, kidney transplantation is the preferred treatment. Only about one third of patients with diabetes who begin dialysis are alive at the end of 5 yr, compared with 75% of such patients who undergo kidney transplantation (30). Transplantation is also the less expensive option and is associated with a greater quality of life (31). Use of a living donor is preferred (32). Patients who opt for a living donor also have the benefit of scheduling their transplant at a convenient time, usually at a point where it is clear they will need a transplant but before they must go on dialysis, whereas deceased kidney donor recipients must wait their turn on the organ transplant list. Currently, the median time to transplant for patients waiting for deceased donor kidneys (which is equal to the number of days by which 50% of patients are transplanted) is about 1200 d (33).

Planning for end-stage kidney disease is best done by referral to a nephrologist. The ideal time to make the referral depends on how well the patient is achieving their goals with respect to blood pressure and management of the comorbidities of progressive kidney disease, but most agree that referral must occur by the time the patient is approaching stage 4 chronic kidney disease, which is defined by the Kidney/Diabetes Outcomes Quality Initiative program as when GFR is between 15 and 29 ml/min. If a patient is planning to go on dialysis or receive a deceased donor organ, an arteriovenous fistula for future hemodialysis should be placed at this time because it requires 6–8 wk to sufficiently mature to provide access.

**Return to the Patient**

In our case, the patient followed a typical course for patients with diabetic nephropathy. Despite excellent control of her glycemia, blood pressure, and lipids, she developed microalbuminuria about 12 yr after diagnosis and experienced a progressive decline in her GFR to stage 4 chronic kidney disease over the next 9 yr. During this time, she also developed both diabetic retinopathy and diabetic neuropathy, and her blood glucose and blood pressure became more difficult to control. At a recent visit, she was also found to have a new anemia and an elevated PTH in the setting of a normal calcium.

Management strategies at this point would include a careful review of her pre- and postmeal glucose, her meal patterns, and her activity. Her hemoglobin A1c is above target, and this information will provide guidance about whether control can be achieved by increasing the glargine alone or, more likely, by adding a short-acting insulin analog at meal times. If her 2-h postmeal glucose values were above 180, we believe she would experience less hypoglycemia if a short-acting insulin analog were added at meal times and she was taught how to adjust her dose based on the carbohydrates she planned to eat at each meal. Adding repaglinide at meal times would be an alternative approach, but given her many years of diabetes that are known to be associated with progressive pancreatic β-cell failure (34), it is unlikely that she will respond well to this secretagogue.

Improving her glycemic control may have benefit on her retinopathy and neuropathy. At this visit, we should reinforce the importance of careful follow-up with her ophthalmologist and daily foot care. The fact that she cannot sense the monofilament increases her risk of developing a foot ulcer, which in turn will increase her risk for amputation. It is important that she understand that foot ulcers can be prevented by daily examination of her feet and the use of appropriate footwear. We would also take this opportunity to refer her to a podiatrist for ongoing foot care and consideration of the use of orthotics. Properly fitted orthotics help unweight pressure points on the foot and can reduce the likelihood of developing foot ulcers and Charcot joints.

The drug regimen used to treat her hypertension must also be reviewed at this time. She is not at target, which places her eyes, kidneys, nerves, and vasculature at risk. Her ACEI should be continued, but thiazide diuretic should be substituted with a loop diuretic because it loses its effectiveness at GFR below 50 ml/min. Loop diuretics not only control the sodium retentive state that worsens as GFR declines but also provides synergistic antiproteinuric effects. If her systolic blood pressure in 1 month is not less than 130 mm Hg, a non-dihydropyridine calcium channel blocker should be added. It is not unusual for patients with diabetes and renal dysfunction to require three or more antihypertensives to control blood pressure. Her serum bicarbonate should be monitored regularly, and sodium bicarbonate should be initiated when it falls less than 22 mEq/liter. This will help bone stability and most recently has been shown to slow the progression of kidney disease (35).

Her LDL cholesterol is above target, and given her risk of cardiovascular disease, she might have a better outcome if it could be lowered. Review of the atorvastatin dose and her adherence to the regimen should be done first to determine whether a change in dosing could bring her LDL to target. A review of her diet and an attempt to lower the fat in her diet would also be indicated. If she is on the maximal dose of atorvastatin, we don’t recommend adding another medication to try to reduce the LDL.
under tight blood pressure control. Nutr Metab Cardiovasc Dis 18: 632–638


