Case Study #1: A 57-Year-Old Man With Type 2 Diabetes, Hypertension, and Microalbuminuria

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Vignette
R.C. is a 57-year-old man with type 2 diabetes first diagnosed 2 years ago. Other medical problems include obesity and hypothyroidism. He has a history of heavy alcohol use but quit drinking alcohol 2 years ago. He denies known drug allergies or reactions. He presents now for routine follow-up and is noted to have a blood pressure of 168/100 mmHg. He is asymptomatic.

Physical exam reveals a height of 5 feet, 8 inches, weight of 243 lb, blood pressure of 160/100 mmHg, and a regular pulse of 84 beats/min. There is no retinopathy or thyromegaly. There is no clinical evidence of congestive heart failure or peripheral vascular disease.

Laboratory evaluation reveals trace protein on urinalysis, blood urea nitrogen of 14 mg/dl, serum creatinine of 1.2 mg/dl, random serum glucose of 169 mg/dl, normal electrolytes, and normal thyroid-stimulating hormone levels. A 24-h urine collection reveals a urinary albumin excretion rate of 250 mg/day.

Questions (answers are listed after the second case commentary)

1. Which of the following is the most appropriate range to target when treating this patient’s blood pressure?
   a. < 150/100
   b. < 150/95
   c. < 140/90
   d. < 130/80
   e. < 120/75
2. Presuming the patient is not currently taking an anti-hypertensive medication, which of the following would be the best first-line drug to manage his blood pressure?
   a. Amlodipine
   b. Hydrochlorothiazide
   c. Irbesartan
   d. Lisinopril
   e. Timolol
3. Which of the following best describes this patient’s renal status?
   a. End stage renal disease
   b. Macroalbuminuria
   c. Microalbuminuria
   d. Normoalbuminuria
   e. Overt nephropathy

Commentary
Diabetic nephropathy is a clinical syndrome characterized by albuminuria, hypertension, and progressive renal insufficiency. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in Western countries, accounting for ~35% of all new ESRD cases in the United States. The life expectancy of patients with diabetic ESRD is <50% at 3 years, despite improvements in dialysis and renal transplantation.

Early detection and treatment of albuminuria is essential in diabetes. The normal rate of albumin excretion is less than 30 mg/day (20 µg/min); persistent albumin excretion between 30 and 300 mg/day (20 to 200 µg/min) is called microalbuminuria and, in patients with diabetes (particularly type 1 diabetes), may be indicative of early diabetic nephropathy. Protein excretion above 300 mg/day (200 µg/min) is considered to represent macroalbuminuria (also called overt proteinuria, overt nephropathy, clinical renal disease, or dipstick positive proteinuria).
Many organizations, including the American Diabetes Association, recommend regular screening for microalbuminuria. People with type 2 diabetes should be screened from the time of diagnosis, since many type 2 diabetic patients have had undiagnosed disease for some time. If the initial screening is negative, then annual screenings are indicated.

Traditional urinary dipsticks are insensitive at detecting albuminuria <300 mg/day. Spot urine samples may be assayed for microalbuminuria and creatinine and a ratio ≥30 µg/mg or mg/g is abnormal. Newer methods, such as Micral-Test II test strips (Boehringer Mannheim, Mannheim, Germany), permit reliable semiquantitative determination of microalbuminuria and can be used in the office for dipstick screening of diabetic patients.

Transient elevations in urinary albumin excretion may be associated with marked hyperglycemia, acute febrile illness, exercise, hypertension, heart failure, and urinary tract infection. If the initial test is elevated, these and other potential causes of renal disease should be considered and ruled out. Because there is also marked day-to-day variability in urinary albumin excretion, a positive test should be confirmed on a subsequent occasion before designating a patient as having persistent microalbuminuria.

Patients identified with persistent microalbuminuria should be aggressively treated both with respect to glycemic and blood pressure control. Patients are considered to be hypertensive if their blood pressure is ≥140/90 mmHg. The goal for the management of hypertensive diabetic patients is to keep the blood pressure <130/80 mmHg.

Once started, renoprotective therapy should be continued indefinitely. ACE inhibitors have been shown to prevent or slow the progression from microalbuminuria to overt nephropathy. Studies have also shown that the renoprotective effects of ACE inhibitors go beyond those expected from blood pressure reduction by itself. Additionally, the renoprotective effects apply to both normotensive and hypertensive patients with microalbuminuria. Therefore, the indication for ACE inhibition can be persistent microalbuminuria, regardless of blood pressure. Discontinuing therapy will result in a recurrence of microalbuminuria.

In addition to aggressively managing blood pressure, attempts need to be made toward lifestyle modifications. These include meticulous control of blood glucose, seeking counseling to stop smoking, maintaining optimal body weight, following an appropriate diet, and exercising regularly.

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**Case Study #2: Treating Hypertension in Patients With Diabetes**

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**Vignette**

L.N. is a 49-year-old white woman with a history of type 2 diabetes, obesity, hypertension, and migraine headaches. The patient was diagnosed with type 2 diabetes 9 years ago when she presented with mild polyuria and polydipsia. L.N. is 5'4" and has always been on the large side, with her weight fluctuating between 165 and 185 lb.

Initial treatment for her diabetes consisted of an oral sulfonylurea with the rapid addition of metformin. Her diabetes has been under fair control with a most recent hemoglobin A1c of 7.4%.

Hypertension was diagnosed 5 years ago when blood pressure (BP) measured in the office was noted to be consistently elevated in the range of 160/90 mmHg on three occasions. L.N. was initially treated with lisinopril, starting at 10 mg daily and increasing to 20 mg daily, yet her BP control has fluctuated.
One year ago, microalbuminuria was detected on an annual urine screen, with 1,943 mg/dl of microalbumin identified on a spot urine sample. L.N. comes into the office today for her usual follow-up visit for diabetes. Physical examination reveals an obese woman with a BP of 154/86 mmHg and a pulse of 78 bpm.

Questions

4. Which of the following presents the greatest risk of morbidity and mortality in this patient?
   a. Cardiovascular disease
   b. Hyperosmolarity
   c. Ketoacidosis
   d. Renal failure
   e. Sepsis

5. Which of the following is the most appropriate approach to managing her blood pressure?
   a. Continue current drug and add hydrochlorothiazide 12.5 mg every AM
   b. Continue current drug, advise achieving a 5 kg weight loss in 3 months and reassess at that time
   c. Decrease dose of current drug and add amlodipine 5 mg every PM
   d. Discontinue current drug and start losartan 50 mg BID
   e. Increase lisinopril to 40 mg every AM

Commentary

Diabetes mellitus is a major risk factor for cardiovascular disease (CVD). Approximately two-thirds of people with diabetes die from complications of CVD. Nearly half of middle-aged people with diabetes have evidence of coronary artery disease (CAD), compared with only one-fourth of people without diabetes in similar populations.

Patients with diabetes are prone to a number of cardiovascular risk factors beyond hyperglycemia. These risk factors, including hypertension, dyslipidemia, and a sedentary lifestyle, are particularly prevalent among patients with diabetes. To reduce the mortality and morbidity from CVD among patients with diabetes, aggressive treatment of glycemic control as well as other cardiovascular risk factors must be initiated.

Studies that have compared antihypertensive treatment in patients with diabetes versus placebo have shown reduced cardiovascular events. The United Kingdom Prospective Diabetes Study (UKPDS), which followed patients with diabetes for an average of 8.5 years, found that patients with tight BP control (< 150/< 85 mmHg) versus less tight control (< 180/< 105 mmHg) had lower rates of myocardial infarction (MI), stroke, and peripheral vascular events. In the UKPDS, each 10-mmHg decrease in mean systolic BP was associated with a 12% reduction in risk for any complication related to diabetes, a 15% reduction for death related to diabetes, and an 11% reduction for MI. Another trial followed patients for 2 years and compared calcium-channel blockers and angiotensin-converting enzyme (ACE) inhibitors, with or without hydrochlorothiazide against placebo and found a significant reduction in acute MI, congestive heart failure, and sudden cardiac death in the intervention group compared to placebo.

The Hypertension Optimal Treatment (HOT) trial has shown that patients assigned to lower BP targets have improved outcomes. In the HOT trial, patients who achieved a diastolic BP of < 80 mmHg benefited the most in terms of reduction of cardiovascular events. Other epidemiological studies have shown that BPs > 120/70 mmHg are associated with increased cardiovascular morbidity and mortality in people with diabetes. The American Diabetes Association has recommended a target BP goal of < 130/80 mmHg. Studies have shown that there is no lower threshold value for BP and that the risk of morbidity and mortality will continue to decrease well into the normal range.

Many classes of drugs have been used in numerous trials to treat patients with hypertension. All classes of drugs have been shown to be superior to placebo in terms of reducing morbidity and mortality. Often, numerous agents (three or more) are needed to achieve specific target levels of BP. Use of almost any drug therapy to reduce hypertension in
patients with diabetes has been shown to be effective in decreasing cardiovascular risk. Keeping in mind that numerous agents are often required to achieve the target level of BP control, recommending specific agents becomes a not-so-simple task. The literature continues to evolve, and individual patient conditions and preferences also must come into play.

While lowering BP by any means will help to reduce cardiovascular morbidity, there is evidence that may help guide the selection of an antihypertensive regimen. The UKPDS showed no significant differences in outcomes for treatment for hypertension using an ACE inhibitor or a β-blocker. In addition, both ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to slow the development and progression of diabetic nephropathy. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitors were found to have a favorable effect in reducing cardiovascular morbidity and mortality, whereas recent trials have shown a renal protective benefit from both ACE inhibitors and ARBs. ACE inhibitors and β-blockers seem to be better than dihydropyridine calcium-channel blockers to reduce MI and heart failure. However, trials using dihydropyridine calcium-channel blockers in combination with ACE inhibitors and β-blockers do not appear to show any increased morbidity or mortality in CVD, as has been implicated in the past for dihydropyridine calcium-channel blockers alone. Recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in high-risk hypertensive patients, including those with diabetes, demonstrated that chlorthalidone, a thiazide-type diuretic, was superior to an ACE inhibitor, lisinopril, in preventing one or more forms of CVD.

L.N. is a typical patient with obesity, diabetes, and hypertension. Her BP control can be improved. To achieve the target BP goal of < 130/80 mmHg, it may be necessary to maximize the dose of the ACE inhibitor and to add a second and perhaps even a third agent.

Diuretics have been shown to have synergistic effects with ACE inhibitors, and one could be added. Because L.N. has migraine headaches as well as diabetic nephropathy, it may be necessary to individualize her treatment. Adding a β-blocker to the ACE inhibitor will certainly help lower her BP and is associated with good evidence to reduce cardiovascular morbidity. The β-blocker may also help to reduce the burden caused by her migraine headaches. Overall, more aggressive treatment to control L.N.'s hypertension will be necessary. Information obtained from recent trials and emerging new pharmacological agents now make it easier to achieve BP control targets.

**Clinical Pearls**

1. Hypertension (blood pressure ≥ 140/90) is a risk factor for cardiovascular complications of diabetes.
2. Clinical trials demonstrate that drug therapy versus placebo will reduce cardiovascular events when treating patients with hypertension and diabetes.
3. A target BP goal of < 130/80 mmHg is recommended for most hypertensive diabetics; < 125/75 is recommended for those with overt nephropathy (if not contraindicated).
4. Pharmacological therapy needs to be individualized to fit patients' needs and may require 2-3 drugs to achieve the blood pressure target.
5. ACE inhibitors, ARBs, diuretics, and β-blockers have all been documented to be effective pharmacological treatment; ACE inhibitors and ARBs are agents best suited to retard progression of nephropathy.
6. Patients with T2DM should be screened for microalbuminuria when diabetes is first diagnosed and annually thereafter.
7. Counsel all diabetic patients on lifestyle modifications, including blood glucose control, weight control, smoking cessation, diet, and exercise.

**Answers to questions:**

1) d  
2) d  
3) c  
4) a  
5) a