CASE STUDIES: IMPROVING CARDIOVASCULAR DISEASE OUTCOMES IN DIABETES*

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The case studies described in this article represent different segments of the diabetes spectrum, with case study 1 illustrating late prediabetes/very early type 2 diabetes and the presence of risk factors for cardiovascular disease, and case study 2 illustrating poorly controlled diabetes, risk factors for cardiovascular disease, and the development of microvascular complications. Both cases underscore the need for comprehensive intervention and reflect how and when nurse practitioners, physician assistants, and other healthcare professionals can intervene to improve cardiovascular disease outcomes in patients with diabetes.

The questions accompanying both case studies include several different management options. Audience responses to each of these options, determined by a show of hands, varied widely, reflecting both a difference of opinion among healthcare professionals and the reality in clinical practice that there is often more than one “right way” to improve outcomes in patients with diabetes.

CASE STUDY 1

**CASE PRESENTATION**

- 28-year-old Mexican American female with a random glucose of 125 mg/dL on a “chemistry panel” obtained as part of an annual health fair; she has no symptoms or prior history of abnormal glucose; a screening oral glucose tolerance test (OGTT) during pregnancy 4 years earlier was negative
  - Past medical history: Negative
  - Medications: None
  - Family history: Mother and brother have type 2 diabetes; mother has history of retinal laser treatments, proteinuria, and foot ulcer
- Social history: Smoker (1 pack a day since the age of 19); owns a convenience store with husband; has 2 children, 4 and 6 years of age
- Review of systems: Frequent yeast infections
- Physical examination
  - Height: 61”
  - Weight: 200 lb
  - Blood pressure: 142/92 mm Hg
  - Waist: 38”
  - Skin tags
  - Trace edema
  - Further examination normal
- Laboratory findings
  - $A_1C$: 6.3% (normal, 4%–6%)
  - 1-hour postprandial glucose: 133 mg/dL

**Question 1**

**What is this patient’s glycemic diagnosis?**

A. 790.21 Impaired fasting glucose
B. 790.22 Impaired glucose tolerance test (oral)
C. 790.29 Other abnormal glucose

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D. 250.00 Type 2 diabetes, well controlled  
E. 277.7 Dysmetabolic syndrome X  
F. None of the above  
G. Other (ie, yeast infection)  

The coding choices—each of which garnered at least a few votes from the audience, although none received a majority—raise several interesting issues.

With regard to choices A and B, it is technically not possible to diagnose impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance (140–199 mg/dL on a 75-g OGTT at 2 hours) in this patient because she never had a fasting glucose determination or a 2-hour OGTT. The problem with choice C is that healthcare providers using the 790.29 code may not be reimbursed for the visit, although it can certainly be argued that a random glucose of 125 mg/dL or even a 1-hour postprandial glucose of 133 mg/dL in a normal individual is higher than expected and thus qualifies as an abnormal glucose level. As for choice D, this patient may very well have type 2 diabetes, but she does not yet meet the diagnostic criteria for the disease (ie, 2 abnormal measures [fasting glucose 126 mg/dL, 2-hour OGTT >200 mg/dL, or random glucose >200 mg/dL with classical symptoms] on 2 separate occasions).

The correct diagnosis for this patient is dysmetabolic syndrome X. She has elevated blood pressure, a waist circumference greater than 35", and an elevated glucose level. Although the diagnostic criteria for this syndrome define a fasting glucose level greater than 110 mg/dL and also include elevated triglycerides and/or low high-density lipoprotein (HDL) cholesterol, it is permissible for a healthcare provider to base this diagnosis on any findings associated with the clinical syndrome. However, the diagnostic code mandates that the diagnosis be made by a “licensed practitioner,” a definition that varies from state to state.

**Question 2**

**Would you do further glucose testing?**

A. No, not this week  
B. Yes, return for a fasting glucose later this week  
C. Yes, return for a 50-g OGTT later this week  
D. Yes, return fasting after at least 3 days on a high-carbohydrate diet (-200 g) for a 75-g OGTT  
E. None of the above

A fasting glucose determination, the option chosen by the majority of the audience, is a perfectly reasonable—and probably the most frequent—way to diagnose diabetes. However, choice D, which garnered a few votes from the audience, is also a reasonable method to detect people with unrecognized diabetes. Although many people taking a 75-g OGTT, which is done after 3 days on a high-carbohydrate diet and a 10-hour fast, try to “pass the test” by cutting back on carbohydrates for 3 days to a week before the test, they are more likely to fail it because they have become somewhat carbohydrate-intolerant during those few days.

**Question 3**

**What would be your first priority in managing this patient?**

A. Smoking cessation counseling  
B. Initiate drug treatment for hypertension  
C. Start a glucose-lowering drug  
D. Take a diet and exercise history; discuss impact of weight loss and exercise on cardiovascular disease risk factors; make specific suggestions regarding lifestyle interventions; discuss plan for follow-up  
E. Check a fasting lipid panel  
F. None of the above

Although at least several members of the audience chose smoking cessation counseling, medication to lower blood pressure or glucose, and checking a fasting lipid panel as their first priority, the overwhelming majority opted for choice D. Addressing all of the components in choice D during a single new patient visit is a fairly complex endeavor that is likely to exceed the time allotted for such a visit. However, this approach enables nurse practitioners, physician assistants, and other primary care providers—and their patients—to focus on the “big picture” and the importance of lifestyle modification with or without medications to lower glucose and/or blood pressure and/or improve the lipid profile.

**Question 4**

**If you start a diabetes drug, which one would be appropriate?**

A. Acarbose or miglitol  
B. Metformin  
C. Pioglitazone or rosiglitazone  
D. Sulfonylurea or nateglinide or repaglinide  
E. Insulin or insulin analog  
F. Exenatide or pramlintide
For this patient, who is on the borderline between late prediabetes and very early diabetes, metformin drew the largest number of audience votes. A few audience members opted for an α-glucosidase inhibitor to slow the absorption of carbohydrate (choice A) or a glitazone or a sulfonylurea, and fewer still opted for choice F; none chose injectable or inhaled insulin.

The use of drugs to treat prediabetes is appropriate, particularly in patients whose glucose levels are slowly increasing despite serious efforts at lifestyle modification. In this scenario, one approach is to order an OGTT as soon as glucose levels start to rise in an attempt to diagnose—and treat—diabetes earlier. Another approach is to use drug therapy in prediabetes when there is a clear rise in glucose and a lack of response to lifestyle interventions. However, none of these treatments are approved by the US Food and Drug Administration for prediabetes.

Trials have shown that the α-glucosidase inhibitors reduce the risk of developing diabetes in individuals with impaired glucose tolerance by approximately 25%, and the Diabetes Prevention Program trial showed that metformin lowered the risk by approximately 30% over 3 years in younger patients with a body mass index more than 35. At present, there are no published reports of clinical studies evaluating treatment with pioglitazone to prevent diabetes, but data from the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) study, which is evaluating rosiglitazone in diabetes prevention, are expected to be presented at major diabetes meetings later this year. (These results were published at the time of publication [DREAM Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368:1096-1105.]) Although previous studies of metolazone have shown that it reduces the risk of developing diabetes by 50% to 75% in high-risk individuals, use of the drug is limited because of concerns about its association with liver toxicity.

As for the remaining treatment options, sulfonylureas, nateglinide, and repaglinide have no role in preventing the progression to diabetes, although they are useful in treating diabetes once it develops. Theoretically, exenatide is a reasonable choice in prediabetes/early diabetes, but treatment involves 2 injections a day. Results from the ongoing Outcome Reduction with an Initial Glargine Intervention trial, which is evaluating insulin and insulin analogs in prediabetes/early diabetes, should be available in 2009.

**Question 5**

If you start a blood pressure medication, which one would be appropriate?

- A. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
- B. Thiazide diuretic
- C. β blocker
- D. Calcium channel blocker
- E. Aldosterone antagonist
- F. Other agent

The vast majority of the audience opted for an ACE inhibitor or ARB therapy to lower this patient's blood pressure, a good choice because there is some evidence that these drugs also reduce the risk of developing diabetes. Data from the DREAM study, which is also evaluating the ACE inhibitor ramipril in prediabetes, will be presented later this year and should elucidate the use of these agents in this setting. (These results were published at the time of publication [DREAM Trial Investigators; Bosch J, Yusuf S, Gerstein HC, et al. Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006;355:1551-1562.].)

A few members of the audience opted for a thiazide diuretic, which is usually the antihypertensive of choice for African Americans. However, in the setting of prediabetes, an ACE inhibitor or ARB would also be appropriate in African Americans.

**Case Disposition**

This patient was never "officially" diagnosed with diabetes, in part because of concerns that the diagnosis would increase her already-high health insurance premiums (because she is self-employed) or even render her uninsurable. However, because of her family history and personal risk factors, she was very well motivated to make the necessary lifestyle modifications to reduce her risk of developing diabetes. She modified her diet—and the family’s—and began an exercise program consisting of a half-hour walk with her husband and children every day after dinner. Over time, she lost 50 pounds. She is still on an ACE inhibitor for her blood pressure, and continues to watch her diet and take a walk after dinner every day. She is doing very well.
CASE STUDY 2

CASE PRESENTATION

- 32-year-old African American male with poorly controlled diabetes diagnosed 10 years earlier when he developed diabetic ketoacidosis during rehabilitation from a spinal cord injury resulting from a car accident; the injury ended his football career
- Current medications: Insulin 70/30, 65 units twice daily
- Glucose levels: Generally mid-200s
- Glucometer download: Average 3.1 readings/day, with mean glucose of 246 mg/dL (± 55 mg/dL)
- Recently started medical nutrition therapy, but says it “doesn’t seem to make a difference”
- Current exercise/physical activity: None
- Past medical history: Fully recovered from spinal cord injury
- Family history: Early vascular disease
- Social history: No alcohol or drug use; ex-smoker (9 pack-years; quit in January 2005); works as a dispatcher for a trucking company; married, with 3 children
- Review of systems: Nocturia; feet are always cold; blurred vision; denies numbness and dysesthesia
- Physical examination
  - Height: 70”
  - Weight: 245 lb
  - Blood pressure: 162/92 mm Hg; pulse 102 bpm
  - Waist: 44”
  - Chest/cardiac examination: Normal
  - Hyperpigmented rash on nape of neck (acanthosis nigricans); skin tags
  - Retina: Cotton-wool spots and hard exudate over macula
  - Oropharynx: Swollen gums with recession
  - Vascular: Left femoral bruit
  - Neurologic: No response to 10-g monofilament
  - Feet: Dry, cracked skin; cock-up deformities
- Laboratory findings
  - $A_1C$: 9.8%
  - Lipids: Total cholesterol, 220 mg/dL; low-density lipoprotein (LDL), 130 mg/dL; high-density lipoprotein (HDL), 30 mg/dL; triglycerides, 300 mg/dL
  - Creatinine: 1.5 mg/dL
  - Blood urea nitrogen: 18 mg/dL
  - Glomerular filtration rate: -70 mL/min
  - Potassium: 4.9 mEq/L
  - Urine microalbumin to creatinine ratio: 232 (normal, <30)
  - Alanine aminotransferase (ALT): 90 IU/L (normal, 50 IU/L)
  - Electrocardiogram: Normal

Question 1
What would be your first priority in managing this patient?
A. Lower glucose/$A_1C$
B. Lower blood pressure
C. Lower cholesterol, specifically LDL
D. Normalize HDL/triglycerides
E. Lifestyle intervention
F. Screen for cardiovascular disease
G. Start an antiplatelet agent
H. Eye care
I. Renal care
J. Screen for depression
K. Other or can’t answer

Audience responses were fairly evenly distributed among the treatment choices, with the exception of lowering blood pressure and LDL, both of which received a few more votes than the other options. The distribution of responses reflects the truth of the matter, which is that this patient is in trouble and all of the treatment choices need to be implemented immediately.

Question 2
Would you order any additional laboratory studies?
A. No, not at this time
B. Lipid profile analysis
C. Timed urine specimen for albumin and creatinine
D. C-peptide
E. Antigliutamic acid decarboxylase antibody
F. C-reactive protein

Only a few members of the audience opted for additional laboratory studies, a perfectly reasonable decision given that this patient has so many problems that need to be addressed immediately. However, because this patient has signs of significant insulin resistance—car-
diovascular risk factors, a huge belly, acanthosis nigricans and skin tags, and poor glucose control despite a high daily insulin dose—a C-peptide determination might be helpful. (In fact, his C-peptide level was found to be 20 ng/mL, confirming extreme insulin resistance and explaining why his high insulin dose was having little effect on his insulin level and his glucose control.)

**Question 3**
**How would you approach this patient’s poor glucose control?**

A. Refer to an endocrinologist  
B. Refer to a certified diabetes educator (CDE)  
C. Consider adding metformin after some additional testing  
D. Consider adding pioglitazone or rosiglitazone after some additional testing  
E. Switch type of insulin regimen  
F. Insulin or insulin analog  
G. Add pramlintide

Although each of the options received at least a few votes from the audience, the trend favored the addition of a glitazone after further testing. In fact, that was the course of action taken for this patient because he is severely insulin resistant.

Referring the patient to an endocrinologist to manage his glucose is a good idea because it enables the nurse practitioner, physician assistant, or other primary care provider to focus on the patient’s other diabetes-related problems. Referring the patient to a CDE for glucose control might be even more reasonable, and for the same reason.

Metformin might help this patient lose some weight, but his high creatinine level is likely to increase and his creatinine clearance is likely to remain at approximately 70 mL/min once he begins therapy to lower his blood pressure. Similarly, switching the type of insulin regimen is not likely to have much impact on glucose control. Increasing the insulin dose would probably require multiple daily injections of an insulin analog. Adding pramlintide is an option, but it will not lower an A1C of 10% to less than 7%.

**Question 4**
**How would you manage this patient’s high blood pressure?**

A. ACE inhibitor or ARB  
B. Thiazide diuretic  
C. Calcium channel blocker  
D. 2-drug combination tablet (with 1 drug being a diuretic)  
E. Lifestyle modification  
F. Refer to a nephrologist

A majority of the audience opted for an ACE inhibitor or ARB, but almost as many chose a thiazide diuretic and a good number cast their votes for a calcium channel blocker. Although all 3 agent classes are effective in lowering blood pressure, this patient needs to be on a combination tablet from the start because his blood pressure is more than 20 points above the accepted target of 130/80 mm Hg. He would also benefit from diet and exercise to lose weight and lower blood pressure. Referral to a nephrologist would also be prudent because, as an African American, he is at increased risk for renal disease.

**Question 5**
**How would you manage this patient’s poor lipid profile?**

A. Initiate a low-dose statin to lower LDL <100 mg/dL  
B. Initiate a low-dose statin to lower LDL <70 mg/dL  
C. Initiate a mid-dose statin to lower LDL <70 mg/dL  
D. Initiate a statin and add niacin or a fibrate  
E. Initiate a statin and hope that HDL and triglycerides will normalize with lifestyle modification, fish oil, pioglitazone, metformin, and/or insulin  
F. Other

Many in the audience opted for choices B and C to lower the LDL less than 70 mg/dL. However given the patient’s initial LDL of 130 mg/dL and his femoral bruit, a mid-dose statin is needed to achieve the lower LDL goal. The addition of lifestyle modifications, pioglitazone, etc (choice E) is also needed because it is likely that these interventions will have a favorable effect on HDL and triglycerides.

Choosing a statin that not only lowers LDL but also lowers triglycerides and raises HDL is an important consideration. However, because this patient’s ALT is already elevated on insulin alone, liver function must be monitored at regular intervals once statin therapy is initiated. A fenofibrate can also be considered if triglyc-
erides remain elevated despite lifestyle modifications, fish oil, a statin, and an antidiabetic drug.

**Case Disposition**

The patient was continued on insulin and given a 2-drug combination tablet to control his blood pressure, a mid-dose statin to lower his LDL, and a glitazone to control his glucose and improve his overall lipid profile. He responded remarkably well to exercise, which independently activates AKT, an enzyme in the insulin pathway. When he exercises, his A1c levels are brought into the 7.2% to 7.4% range. However, when he cannot exercise because of foot ulcers, his blood glucose increases.

**Key Treatment Points**

Treating prediabetes and diabetes to improve cardiovascular outcomes requires a comprehensive approach that addresses glucose control, blood pressure control, and normalization of the overall lipid profile. In prediabetes in particular, this 3-pronged approach should also assess the patient’s motivation to make lifestyle changes. Many patients with prediabetes are well motivated and eager to do whatever is necessary to avoid developing diabetes.

Glucose control begins with screening for elevated glucose levels, making the diagnosis as early as possible, initiating lifestyle interventions, and establishing target glucose levels. Insulin-resistant patients may need to be treated with an insulin-sensitizing agent, such as a thiazolidinedione or metformin. Patients with very high fasting glucose levels should also be evaluated for insulin deficiency and treated with a sulfonylurea, insulin, or exenatide. Those patients with satisfactory fasting glucose levels but A1c levels that remain above the established goal may require treatment with an agent that targets postprandial glucose and can lower glucose with little risk of causing hypoglycemia.

Lifestyle intervention, such as weight loss, exercise, and smoking cessation, are extremely effective in lowering blood pressure to lower than 130/80 mm Hg, the goal established by the American Diabetes Association. Pharmacologic therapy is indicated if the systolic and/or diastolic blood pressure goals are not met. ACE inhibitors and ARBs are particularly helpful in patients with albuminuria, cardiovascular risk factors, and/or diabetes. A 2-drug combination tablet that includes a thiazide diuretic is especially useful in patients with renal or heart disease, as the diuretic lowers blood pressure by reducing volume.

With regard to normalization of the lipid profile, it is recommended that most patients with diabetes be treated with a statin regardless of their LDL cholesterol level. Goal LDL levels are lower than 100 mg/dL for all patients and lower than 70 mg/dL for those at highest risk for a cardiovascular event. Glucose-lowering agents, such as pioglitazone, metformin, and insulin, are quite effective in managing diabetic dyslipidemia, as are fibrates, niacin, fish oil, and the statins.

**References**