Controversies in Treating Pre-Diabetes

by Edward J. Shahady, MD

CASE PRESENTATION Diabetes and pre-diabetes are common problems encountered in the daily practice of a primary care clinician. Multiple well-accepted treatment options are available for diabetes treatment but pre-diabetes treatment is more challenging. The following case and the clinical decision making associated with it highlight many of these challenges.

A 42-year-old man comes to your office for a routine checkup. He has no complaints and just wants to be sure he is OK. His paternal uncle had type 2 diabetes and his father sustained a myocardial infarction at age 44. His exam reveals a body mass index (BMI) of 28, waist circumference of 42 inches and blood pressure of 142/90 mm Hg. His laboratory tests were as follows: total cholesterol, 200 mg/dL; triglycerides, 350 mg/dL; low-density lipoprotein cholesterol (LDL-C), 100 mg/dL; high-density lipoprotein cholesterol (HDL-C), 30 mg/dL; fasting blood sugar, 115 mg/dL; and non-HDL-C, 170 mg/dL. Complete blood count, renal function and liver function tests were all normal. Additional studies included a two-hour postprandial glucose of 155 mg/dL and hemoglobin A1c (HbA1c) of 5.7%.

Which of the following treatment options would you choose to prevent the onset of diabetes? (One or more options may be chosen.)

A. Lifestyle changes (nutritional advice and exercise)
B. Metformin (Glucophage)
C. Thiazolidinediones (Pioglitazone [Actos], Rosiglitazone [Avandia])
D. Statins

This patient is at high risk of developing type 2 diabetes as indicated by his fasting and postprandial glucose, elevated triglycerides, and decreased HDL-C. Evidence from the Diabetes Prevention Program Research Group[1] trial indicates that option A (lifestyle changes) is a very effective means of decreasing the onset of diabetes. This randomized trial of high-risk patients—similar to the patient described above—demonstrated that a 7% weight loss and at least 150 minutes of physical activity per week reduced the incidence of diabetes by 58% compared to placebo. This same study demonstrated that compared to placebo, option B (metformin) decreased the incidence of pre-diabetes by 31%. Two other trials demonstrated that option C (thiazolidinediones) reduced the risk of developing diabetes in high-risk individuals by 55% and 60%.[2,3] Option D (statins) is not known to prevent the onset of diabetes. Option A is well-accepted as the treatment of choice for pre-diabetes.

Although evidence exists that pharmacological options (B and C) exist to prevent diabetes, there is no agreement in the medical community that pre-diabetes alone is sufficient reason to justify their use.

The clinician is left with a challenge. Lifestyle changes are a logical choice, but what about the additional use of pharmacological agents? This challenge is even greater with the addition of the newer drugs like exenatide (Byetta) and sitagliptin (Januvia) that may preserve β-cell function. Although it is tempting to add a pharmacological agent, the risks must be balanced by the benefits. In the patient described above—who may live another 40 years—are these drugs safe to take for 40 years? On the other hand, delaying or preventing the devastating consequences of diabetes may more than balance the risk. It is also a given that many patients have difficulty achieving and/or sustaining lifestyle changes. If the clinician has done an effective job of motivating the patient and utilized all the resources that are available to the patient (nutritional and exercise counseling), pharmacological management may be indicated if the patient is at significant risk of developing diabetes and cardiovascular disease (CVD). Patients who are not at significant risk may not be candidates for pharmacological management.

TABLE 1 Hazard Ratios of Developing Coronary Heart Disease or Diabetes by Number of Characteristics of the Metabolic Syndrome

Elements of the Metabolic Syndrome	CHD	Diabetes
0	1	1
1	1.79	2.36
2	2.25	4.50
3	3.19	7.26
≥4	3.65	24.4

Source: Adapted from Sattar N, Gaw A, Scherbakova O et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003;108:414-419.[7] Adapted with permission.

The patient has all the elements of the metabolic syndrome with an increased waist circumference, hypertension, high triglycerides, low HDL-C and elevated fasting blood sugar. These are the five elements of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP).[4] Although some controversy exists around the use of this term, it still serves as a useful way of recognizing the clustering of risk factors that indicate cardiometabolic risk.[5,6] Each one of these factors taken individually is associated with increased risk of CVD and as more risk factors are added, the greater the risk of developing diabetes and coronary heart disease (CHD) (**Table 1**).[7] The risk of developing diabetes is 24 times greater and CHD is 3.6 times greater when a person has all five elements of the metabolic syndrome present. This patient has all five elements of the metabolic syndrome and a significant family history of diabetes and premature CVD.

Adding a pharmacological agent should be considered given his degree of risk. Metformin is the least expensive of the above choices; it has been used for some time, has known effects on diabetes prevention,[1] positive effects on lipids[8] and decreases CVD.[9] It is a reasonably safe drug, well tolerated in most patients and has been in use for over 10 years. A recent American Diabetes Association consensus statement provides guidelines for considering the use of metformin when impaired glucose tolerance exists (**Table 2**).[10] The patient meets these criteria. Thiazolidinediones are equally effective as metformin but are more expensive and are associated with edema. With the above reasoning, I choose options A and B.

After six months of lifestyle changes, metformin 1000 mg/day, lisinopril (Prinivil, Zestril) 5 mg/day and 81 mg of ASA daily, the patient returned for follow-up care. He reported that he was walking two to three days a week and was trying his best to limit fast foods. His weight had decreased by 5 lb. His exam reveals a BMI of 27, waist circumference

TABLE 2

The American Diabetes Association consensus panel recommends lifestyle modification and metformin (850 mg twice per day) if the patient has IFG (FPG ≥100 mg/dL and <126 mg/dL) or IGT two-hour postprandial (≥140 mg/dL and <200 mg/dL) and any one of the following:

- <60 years of age
- BMI ≥35 kg/m^2
- Family history of diabetes in first-degree relatives
- Elevated triglycerides
- Reduced HDL-C
- Hypertension
- HbA1c >6.0%

IFG = impaired fasting glucose; FPG = fasting plasma glucose; IGT = impaired glucose tolerance

Source: Adapted from Nathan DM et al.[10] Copyright© 2007 American Diabetes Association From Diabetes Care®, Vol. 30, 2007; 753-759. Reprinted with permission from the *American Diabetes Association.*

of 41 inches and blood pressure of 133/84 mm Hg. Laboratory tests were as follows: total cholesterol, 200 mg/dL; triglycerides, 250 mg/dL; LDL-C, 118 mg/dL; HDL-C, 32 mg/dL; fasting blood sugar, 115 mg/dL; and non-HDL-C, 168 mg/dL. Complete blood count, renal function and liver function tests were all normal.

You will note that his LDL-C increased from 100 mg/dL to 118 mg/dL but total cholesterol remained at 200 mg/dL. At first glance, his original LDL-C level seemed reasonable at 100 mg/dL but this is misleading because it is a calculated value. The LDL-C level obtained in most lipid profiles is calculated using the Friedewald formula.[11] This formula (Total cholesterol - HDL - triglycerides/5) creates a false impression by underestimating the LDL-C when the triglycerides are high. When first seen the calculation of 200 - 30 - 300/5=100 and six months later the calculation was 200 - 32 - 250/5=118. Low-density lipoprotein cholesterol levels are not valid for therapeutic decisions when triglycerides are over 200 mg/dL.[4] Non-HDL-C becomes the therapeutic target when this occurs.[4] Non-HDL-C is a simple no-cost test. Once you have the usual lipid profile, calculate non-HDL-C by subtracting the HDL-C from the total cholesterol (e.g., 200-32=168 mg/dL).

This patient has atherogenic dyslipidemia (high triglyceride and low HDL-C levels). This combination indicates a high concentration of small, dense LDL-C that is highly atherogenic. Non-HDL-C levels are excellent indicators of the number of small dense LDL-C atherogenic particles that are present.

The non-HDL-C goal in patients with moderately high CVD risk is <130 mg/dL and <100 mg/dL in patients with very high CVD risk factors.[4] Non-HDL-C predicts CVD in patients with diabetes[12] and non-HDL-C may be superior to LDL-C in predicting CVD in patients with diabetes.[13] Non-HDL-C contains the highly atherogenic small, dense lipoproteins that are associated with a high incidence of CVD.[14]

Which of the following options would you now choose for treating his lipids? (One or more options may be chosen.)

A. Obtain a hsCRP value
B. Start a statin
C. Start a fibrate
D. Start niacin
E. Start no new drugs and continue the above treatment to see if he continues to improve

Option A is a helpful choice. High-sensitivity C-reactive protein (hsCRP) is a surrogate marker for inflammation and cardiovascular risk. Levels of hsCRP of ≥3 mg/L predict future cardiovascular events[15] and can help stratify risk levels in patients with the metabolic syndrome.[7] The more elements of the metabolic syndrome that are present, the greater risk of a cardiovascular event. This patient's hsCRP level was 4 mg/L. If this level is not elevated the clinician can feel comfortable not being aggressive with further treatment. With an elevated level of 4 mg/L more aggressive therapy seems indicated. For this reason option E was not chosen.

The patient's non-HDL-C is also elevated at 168 mg/dL. Unfortunately most physicians are not aggressive in treating non-HDL-C.[16] **Table 3** compares goal achievement of LDL-C with non-HDL-C in both moderate and very high risk patients from the NCEP Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II national survey.[17] This national survey included patients with triglycerides >200 mg/dL who were undergoing outpatient lipid management. Goal achievement for non-HDL-C was lower than LDL-C

TABLE 3 Achievement of LDL-C and Non-HDL-C Goals by Risk Category

Patient Category	Achieved LDL-C goal	Achieved Non-HDL-C goal
Moderately high risk	38%	23%
Very high risk	23%	4%

Source: Shahady E (2007). Data from Davidson MH et al.[17]

goal achievement especially for patients in the very high risk group.

Choosing an option that will lower non-HDL-C is now indicated. All three of the remaining options (statin, fibrate, niacin) will accomplish that goal. Statins will lower LDL-C up to 60%, produce a small (4% to 5%) increase in HDL-C and decrease triglycerides 20% to 30%. Fibrates will lower triglycerides up to 35%, raise HDL-C 5% to 15% and increase LDL-C 5% to 6%. Niacin reduces LDL-C 30% to 40%, decreases triglycerides 19% to 35% and increases HDL-C 18% to 45%. Statins and niacin are associated with a reduction in cardiovascular events, with statins showing the greatest reduction in events. Fibrates have shown some risk reduction in selected populations.[18]

In addition to continuing lifestyle changes, I choose option B (statins). The superior reduction in LDL-C and greater reduction in cardiovascular events with statins influenced the decision.

> Six months later the patient returned. His weight had decreased by 8 lb and his lipid profile was as follows: total cholesterol, 150 mg/dL; triglycerides, 150 mg/dL; HDL-C, 40 mg/dL; LDL-C, 80 mg/dL (calculated); and non-HDL-C, 110 mg/dL.

(At press time, the U.S. Food and Drug Administration had not decided to add a black box warning to rosiglitazone. A joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on July 30, 2007, resulted in a 22-1 vote to keep the medication on the market and a 20-3 vote that evidence shows the drug adds to risks of heart attacks—Ed.)

References

1. Knowler WC, Barrett-Connor E, Fowler SE et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.
2. Buchanan TA, Xiang AH, Peters RK et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes.* 2002;51:2796-2803.
3. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. [Published erratum in *Lancet.* 368:1770.] *Lancet.* 2006;368:1096-1105.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
5. Kahn R, Buse J, Ferrannini E, Stern M; American Diabetes Association; European Association for the Study of Diabetes. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2005;28:2289-2304.
6. Kahn R. Metabolic syndrome: is it a syndrome? Does it matter? *Circulation.* 2007;115:1806-1811.
7. Sattar N, Gaw A, Scherbakova O et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation.* 2003;108:414-419.
8. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). [Published erratum in *Lancet.* 352:1558.] *Lancet.* 1998;352:854-865.
9. Robinson AC, Burke J, Robinson S et al. The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control. *Diabetes Care.* 1998;21:701-705.
10. Nathan DM, Davidson MB, DeFronzo RA et al.; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care.* 2007;30:753-759.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.
12. Lu W, Resnick HE, Jablonski KA et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care.* 2003;26:16-23.
13. Wang CY, Chang TC. Non-HDL cholesterol level is reliable to be an early predictor for vascular inflammation in type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2004;89:4762-4767.
14. Krauss RM. Atherogenicity of triglyceride-rich lipoproteins. *Am J Cardiol.* 1998;81:13B-17B.
15. Nash DT. C-reactive protein: a promising new marker of cardiovascular risk? *Consultant.* 2005:45;453-460.
16. Maki KC, Galant R, Davidson MH. Non-high-density lipoprotein cholesterol: the forgotten therapeutic target. *Am J Cardiol.* 2005;96:59K-64K.
17. Davidson MH, Maki KC, Pearson TA et al. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey: implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol.* 2005;96:556-563.
18. McKenney JM. Effects of drugs on high-density lipoprotein. *Journal of Clinical Lipidology.* 2007;1:74-87.