THE LINK BETWEEN TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

Based on a presentation by Bartol TG
Richmond Area Health Center, Richmond, Maine and Husson College School of Nursing, Bangor, Maine

The relationship between diabetes and cardiovascular disease (CVD), particularly atherosclerosis, is amply demonstrated by recent mortality and morbidity statistics. Approximately 80% of all mortality in persons with diabetes is because of atherosclerosis of the coronary arteries and cerebral or peripheral vessels. Atherosclerosis also accounts for over 75% of all hospitalizations for diabetic complications, and cardiovascular complications account for approximately 50% of the costs of inpatient diabetes care. In fact, the link between atherosclerosis and diabetes is so strong that the National Cholesterol Education Program designated diabetes as a "coronary artery disease risk equivalent," meaning that a person with diabetes and a person who has already had a heart attack have the same risk for death from a cardiovascular cause.

Diabetes and CVD develop over time, thus providing a window for interventions to prevent both diseases and/or delay their progression. In light of the rising incidence of diabetes, clinicians must keep diabetes risk in mind in all patients—regardless of their presenting complaints—and consider further evaluation and then intervention or referral of patients.

UNDERLYING DEFECTS OF TYPE 2 DIABETES

Three major underlying defects help to explain how prediabetes progresses to type 2 diabetes and how diabetes increases the risk for CVD: insulin resistance, increased hepatic glucose output, and decreased pancreatic insulin secretion.

Insulin resistance, which is present in approximately 92% of people with type 2 diabetes, precedes the manifestations of type 2 diabetes, often by several years. Insulin resistance occurs primarily in fat and muscle cells and, to a lesser extent, in liver cells. The normal glucose-lowering effect of insulin on these cells is blunted, resulting in mildly elevated blood glucose levels. The pancreas responds to the rise in blood glucose by providing increased insulin, resulting in hyperinsulinemia and normoglycemia. Over time, the pancreas produces increasing amounts of insulin to maintain normoglycemia.

As long as the pancreas can produce enough insulin, blood glucose will remain at normal levels. In fact, blood glucose levels in people with hyperinsulinemia are normal because the pancreas is working overtime to maintain homeostasis. However, when the pancreas can no longer maintain normoglycemia, blood glucose levels start to rise, resulting in a relative insulin deficiency and the prediabetes state. Insulin production begins to drop off and blood glucose levels increase; eventually, diabetes occurs. When most people are first diagnosed with type 2 diabetes, they are...
producing more than the average amount of insulin, but they have a relative insulin deficiency because the amount of insulin produced is no longer adequate to maintain normoglycemia.

Changes in insulin and glucose levels over time—from normoglycemia, through the insulin-resistant state and then to prediabetes or impaired glucose tolerance, to diabetes—are shown in Figure 1. The goal is to intervene when insulin levels begin to rise but glucose levels remain normal.

Hyperinsulinemia stimulates fat storage, increases appetite, increases sodium reabsorption in the kidneys, decreases fibrinolysis, and is associated with vascular inflammation and endothelial dysfunction. It also has been identified as an independent predictor of ischemic heart disease, regardless of lipid levels, smoking, and hypertension.4 Clinical markers of hyperinsulinemia include high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels, elevated blood pressure, and central obesity.

Increased hepatic glucose output results in increased glycogen production and gluconeogenesis, and fasting hyperglycemia as a result of hepatic insulin resistance. In this scenario, the liver produces extra glucose, typically in the fasting state. This explains why some people with a blood glucose level of 160 mg/dL after supper will have a fasting glucose level of 220 mg/dL the next morning.

Decreased pancreatic insulin secretion occurs when the pancreas can no longer continue producing high amounts of insulin to maintain normoglycemia. As insulin levels begin to decrease, glucose levels begin to rise. The absolute insulin level is still above normal, but there is a relative insulin deficiency. As glucose levels rise, they impair β-cell production of insulin, resulting in further insulin deficiency and hyperglycemia.

INSULIN RESISTANCE, DIABETES, AND CARDIOVASCULAR RISK

Diabetes is associated with several well-recognized risk factors for CVD, including lipid abnormalities and hypertension. However, insulin resistance also is associated with several risk factors for CVD, including hypertension, hyperinsulinemia, increased blood viscosity, microalbuminuria, lipid abnormalities, and the presence of small, dense, and highly atherogenic low-density lipoprotein cholesterol (LDL-C) particles.5

Insulin resistance and prediabetes may occur 5 to 10 years or more before type 2 diabetes is diagnosed. The onset of microvascular complications can occur several years before the diagnosis of type 2 diabetes. Macrovascular complications may occur even earlier. Thus, it is important to assess patients for diabetes and its precursors early to prevent these chronic complications from occurring.

TREATING DIABETES AND PREDIABETES

Treatment of diabetes and prediabetes requires intervention to lower glucose, lower blood pressure, and normalize lipid levels. Each can be accomplished by dietary changes, exercise, and other lifestyle modifications, but the first priority must be to help motivate patients to change. Small changes in diet or even a modest increase in exercise or physical activity can be a helpful first step. Drugs and multidrug therapies to control glucose, blood pressure, and lipids should be initiated when necessary, and all patients with diabetes should take at least 81 mg of acetylsalicylic acid each day to lower their risk for CVD.

IMPACT OF CURRENT DIABETES THERAPIES ON MACROVASCULAR OUTCOMES

Based on a presentation by Wysham CH Rockwood Clinic, Spokane, Washington

Type 2 diabetes and CVD are linked by several risk factors that contribute to both diseases. These risk factors include lipid abnormalities, elevated blood pressure, elevated blood glucose, and other cardiovascular
risk factors associated with insulin resistance. Because many studies have shown that controlling these risk factors reduces the risk of macrovascular complications in people with diabetes, treatment should be directed at all of the risk factors instead of glucose alone.

**CONTROLLING LIPIDS AND BLOOD PRESSURE**

The landmark statin studies conducted in the 1990s demonstrated that lowering total and LDL-C reduced the risk of cardiovascular events by 25% to 30% in subjects with and without diabetes, alike. More recently, 2 placebo-controlled studies evaluating 2 different statins showed that lowering LDL with these drugs reduced cardiovascular event rates by 20% to 33% in subjects with diabetes. These findings have convinced many healthcare professionals that all patients with diabetes—particularly type 2 diabetes—should be receiving statin therapy.

Studies evaluating the effects of fibrates on normalizing lipids and reducing cardiovascular risk found more modest reductions in cardiovascular events (11%–22%), increased levels of HDL-C, and decreased levels of triglycerides.

Several studies have demonstrated that lowering blood pressure markedly reduces the risk of death from cardiovascular causes. In fact, several major hypertension studies showed that patients with diabetes often derived greater benefit from blood pressure reduction than patients who did not have diabetes. On average, these studies found that a reduction of approximately 10 mm Hg significantly reduced cardiovascular risk.

For example, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight control of blood pressure with an angiotensin-converting enzyme (ACE) inhibitor or a β blocker significantly reduced the risk of microvascular and macrovascular complications by 21% to 56% versus less tight control in patients with hypertension and type 2 diabetes. Mean blood pressure during follow-up, which extended for a median of 8.4 years, was significantly reduced from a mean of 160/94 mm Hg at study entry to 144/82 mm Hg in patients assigned to tight control and to 154/87 mm Hg to those assigned to less tight control.

**GLUCOSE CONTROL**

Glucose control, through diet and/or glucose-lowering agents, is essential in managing diabetes and reducing the risk of cardiovascular events and macrovascular complications. However, lowering glucose without controlling elevated blood pressure and dyslipidemia will not reduce cardiovascular risk to the extent that it needs to be reduced.

The UKPDS found that intensive glucose lowering with a sulfonylurea or insulin versus diet substantially reduced the risk of microvascular complications in patients with type 2 diabetes, but the overall reduction in myocardial infarction (MI) of 16% at 10 years did not reach statistical significance. However, the Diabetes Control and Complications Trial (DCCT) and its extension, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated an interesting phenomenon with regard to risk for macrovascular complications. In the DCCT, it was clear that after a mean follow-up of 6.5 years that intensive therapy (insulin pump or ≥3 daily injections plus frequent blood glucose monitoring) markedly reduced the risk for microvascular complications by 35% to 90% compared to conventional therapy (1 or 2 daily injections). Because very few patients in either group had macrovascular complications, there was no significant difference between the groups in terms of risk reduction.

When the DCCT closed, study patients were followed in the 7-year observational EDIC study; individuals who had completed conventional therapy and had average glycosylated hemoglobin (HbA1c) levels of approximately 9% (vs 7.3% in individuals receiving intensive therapy) were encouraged to switch to intensive treatment. After approximately 1 year, HbA1c levels in patients initially randomized to intensive therapy and in those who had switched from conventional therapy averaged approximately 8%, where they remained for the rest of the EDIC study.

What emerged over the course of the EDIC study was that the longer patients remained in the study, the greater their reduction in risk for macrovascular complications. In the most recently published EDIC report, patients initially randomized to intensive therapy had a 57% reduction in macrovascular events compared to patients initially randomized to conventional therapy, even though the average HbA1c levels were essentially identical in both groups over the previous 7 years.

Whereas the EDIC findings suggest that the risk reductions conferred by intensive glucose therapy in the DCCT persist over time, the findings also suggest that better glucose control is still needed to reduce the
risk of macrovascular complications to the lowest possible level.

**Multifactorial Intervention**

The Steno-2 study investigated the effects of multiple risk factor intervention on microvascular and macrovascular complications in patients with type 2 diabetes and albuminuria at the Steno Diabetes Center in Copenhagen, Denmark. Patients were randomized to conventional therapy, which followed Danish national guidelines, or intensive therapy, which used a stepwise implementation of behavior modification, pharmacologic therapy to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, and daily acetylsalicylic acid for the secondary prevention of CVD.

After a mean follow-up time of 7.8 years, patients who received intensive therapy had lowered their HbA1c levels from 8.6% to approximately 7.8%, which was an improvement, but higher than the study goal of less than 6.5%. Their systolic blood pressure (132 mm Hg), LDL-C (75 mg/dL), and triglyceride levels (150 mg/dL) were well controlled. By comparison, patients who received conventional therapy demonstrated a rise in HbA1c to approximately 9% and poorly controlled systolic blood pressure (148 mm Hg), LDL (130 mg/dL), and triglyceride levels (260 mg/dL).

The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, or amputation. Whereas 55% of patients receiving conventional therapy suffered 1 or more of these macrovascular events by study’s end, patients receiving intensive therapy had a 53% reduction in risk for these events. The study thus demonstrates that intensive therapy of multiple risk factors is highly effective in reducing risk for cardiovascular events and better glucose and blood pressure control should reduce risk even further.

**Insulin Resistance and Other Cardiovascular Risk Factors**

Other risk factors for CVD that require intervention in patients with diabetes include overweight/obesity, smoking, sedentary lifestyle, endothelial dysfunction and inflammation, coagulation, and insulin resistance.

Insulin resistance is associated with several traditional and nontraditional risk factors for CVD. These risk factors include type 2 diabetes and glycemic disorders, such as impaired glucose tolerance or impaired fasting glucose, dyslipidemia, hypertension, endothelial dysfunction and inflammation, and impaired thrombosis. All are involved in the development of atherosclerosis.

Many, but not all, patients who are insulin resistant have an increased waist circumference (ie, a big belly). However, although increased waist circumference and body mass index strongly suggest insulin resistance, they are not diagnostic. What really matters is how much fat is within the visera as opposed to how much fat is outside the abdominal cavity (ie, subcutaneous).

The disparity in visceral and subcutaneous fat, and the reason obesity and insulin resistance are such strong risk factors for diabetes, can be explained by the overflow hypothesis, which holds that adipocytes represent a storage depot for energy (ie, fat). When the capacity of these cells to store fat in the subcutaneous tissues is outstripped by excessive food intake, the excess fat overflows into muscle where it causes resistance to the action of insulin, into the liver where it promotes hepatic gluconeogenesis, and into the pancreas where it is associated with decreased insulin secretion.

Adipocytes themselves produce several different proteins that profoundly influence insulin sensitivity and glucose metabolism and are involved in insulin resistance, β-cell dysfunction, and endothelial dysfunction and inflammation. Several of these proteins can be favorably altered by pharmacologic and nonpharmacologic interventions to improve insulin sensitivity.

**Improving Insulin Sensitivity**

Improving insulin sensitivity is instrumental in the management of diabetes and in the prevention of progression from prediabetes to diabetes. Insulin resistance is reduced by weight loss—through calorie and fat restriction and increased exercise—and/or medications, primarily metformin and the glitazones.

Metformin is a modest insulin sensitizer that acts primarily on the liver to decrease basal and insulin-mediated suppression of hepatic glucose output. As such, it lowers HbA1c levels by 1% to 2%. Metformin also has favorable effects on lipids, blood pressure, microalbuminuria, inflammation, blood clotting, vascular reactivity, and endothelial function.

In a UKPDS substudy of patients with obesity who participated in a large study comparing intensive ver-
sus conventional glucose control, intensive therapy with metformin plus diet was associated with a 32% reduction in any diabetes-related endpoint, including microvascular and macrovascular complications, and a 39% reduction in MI.11,19

The thiazolidinediones (TZDs), or glitazones, work through the peroxisome proliferator-activated receptor γ (PPARγ) system, which is abundant in adipose tissue and thought to be a master switch in adipogenesis, lipid metabolism, and glucose control. PPARγ and its co-activator work at the gene level to promote a protein transcription product that favorably affects fat cells, lipid metabolism, insulin sensitivity, and blood vessel walls. As shown in Figure 2, PPARγ activation helps redistribute fat from the viscera to outside the abdominal cavity and just underneath the skin.

A study examining the effect of pioglitazone on abdominal fat distribution found a 10% reduction in the visceral fat area, a 15% increase in the subcutaneous fat area, and a marked improvement in the visceral to subcutaneous fat ratio.20 In addition, a study comparing rosiglitazone with metformin in patients with increased hepatic fat found that the glitazone reduced the amount of fat in the liver by 51% (vs a slight increase in fat in the metformin-treated group).21 This finding is significant because there is a growing body of evidence suggesting that intrahepatic fat may be one of the earliest changes that occur in patients with metabolic syndrome or insulin resistance.

The favorable changes in visceral and subcutaneous fat with PPARγ activation result in less resistance to insulin action in the liver, muscle, and adipose tissue. This, in turn, leads to decreased glucose production, increased glucose uptake, and improved β-cell secretion in the pancreas. The net result is less vascular inflammation, a cardiovascular benefit. The glitazones also have favorable effects on lipids, blood pressure, thrombolysis, and endothelial cell function.22,23

The Prospective Pioglitazone Clinical Trial in Macrovascular Events was specifically designed to evaluate the effects of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease.24 More than 5200 patients were recruited and assigned to pioglitazone or placebo to be taken in addition to their usual glucose-lowering drugs and other medications. The primary endpoint was the composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The secondary endpoint was the composite of all-cause mortality, nonfatal MI, and stroke.

There were highly significant differences between the treatment and placebo groups with regard to HbA1c, triglycerides, LDL, HDL, and LDL/HDL from baseline to the last visit,24 with most of the differences favoring treatment with pioglitazone. Although the 10% reduction in risk in the treatment group for the primary composite endpoint was not statistically significant, the 16% reduction in the predefined secondary composite endpoint of stroke, MI, and all-cause mortality in the treatment group was. It has been suggested that this 16% reduction reflects the effects of pioglitazone on HbA1c, triglycerides, and HDL rather than its impact on insulin resistance. Many also think that the study population, with macrovascular disease already present, may not have been able to benefit from TZD/glitazone therapy because they were too far advanced in the spectrum of disease. Therefore, the possibility of greater benefit with glitazones in primary prevention cannot be ruled out.
CASE STUDIES: IMPROVING CARDIOVASCULAR DISEASE OUTCOMES IN DIABETES
Reviewed by Bartol TG
Richmond Area Health Center, Richmond, Maine and Husson College School of Nursing, Bangor, Maine
Based on a presentation by Buse JB
University of North Carolina School of Medicine, Chapel Hill, North Carolina

CASE 1
The first case involves a 28-year-old Mexican American woman with a random glucose of 125 mg/dL obtained at an annual health fair. She is 61” tall, weighs 200 lb, and has a waist circumference of 38”; her blood pressure is 142/92 mm Hg. She has a family history of type 2 diabetes and a personal history of frequent yeast infections. She has smoked a pack of cigarettes a day since the age of 19. Laboratory findings reveal an HbA1c of 6.3% (normal, 4%–6%) and a 1-hour postprandial glucose of 133 mg/dL.

MANAGEMENT ISSUES AND OPTIONS
At issue are this patient’s glycemic diagnosis, the need for further glucose testing, whether drug therapy is necessary to control her glucose and blood pressure, and if so, which agents would be most appropriate.

Because this patient never had a fasting glucose determination or a 75-g oral glucose tolerance test (OGTT) at 2 hours, it is technically not possible to diagnose impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes. She does not yet meet the diagnostic criteria for type 2 diabetes, which requires 2 abnormal glucose measures on 2 separate occasions. However, she does have elevated blood pressure, a waist circumference greater than 35”, elevated triglycerides, and low HDL-C, thereby meeting the diagnostic criteria for dysmetabolic syndrome X.

The usual course for a patient such as this one is to obtain a fasting blood glucose determination or a 75-g OGTT at 2 hours, it is technically not possible to diagnose impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes. She does not yet meet the diagnostic criteria for type 2 diabetes, which requires 2 abnormal glucose measures on 2 separate occasions. However, she does have elevated blood pressure, a waist circumference greater than 35”, elevated triglycerides, and low HDL-C, thereby meeting the diagnostic criteria for dysmetabolic syndrome X.

The usual course for a patient such as this one is to obtain a fasting blood glucose determination, although a 75-g OGTT, which is done after 3 days on a high-carbohydrate diet and a 10-hour fast, is also an option. It is also necessary to provide smoking cessation counseling, make specific suggestions regarding dietary and exercise modifications, check a fasting lipid panel, and consider drug therapy to lower glucose and blood pressure.

Glucose-lowering therapy is appropriate for this patient, who is on the border between late prediabetes and very early type 2 diabetes. Metformin is frequently prescribed in these circumstances. Other agents, such as acarbose and the glitazones, are prescribed less often. Theoretically, exenatide is a reasonable choice, but treatment involves 2 injections a day. The sulfonylureas, nateglinide and repaglinide, have no role in preventing the progression of prediabetes to diabetes, although they are useful once diabetes develops. However, none of these treatments are approved by the US Food and Drug Administration for prediabetes.

Drug therapy to lower her blood pressure is also appropriate. An ACE inhibitor or an angiotensin II receptor blocker (ARB) is a good choice, particularly because they also protect the kidney.

CASE DISPOSITION
This patient was never “officially” diagnosed with diabetes because a fasting glucose determination was never obtained, but she was given an ACE inhibitor to lower her blood pressure. 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 took a half-hour walk every evening after supper. Over time, she lost 50 lb. She is still on an ACE inhibitor for her blood pressure, and continues to watch her diet and take a walk every day. She is doing very well.

CASE 2
This case involves a 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. He is currently on insulin 70/30 (65 U twice a day) and his glucose levels are generally in the mid-200s. He is an ex-smoker, does not get any regular exercise, and has a family history of vascular disease. He recently started medical nutrition therapy, but says it has not helped. He reports nocturia, blurred vision, and cold feet, but denies any numbness and dysesthesia.

He is 70” tall, weighs 245 lb, and has a waist circumference of 44”; his blood pressure is 162/92 mm Hg. He has a hyperpigmented rash on the nape of his neck, cotton-wool spots and hard exudate over the macula, a left femoral bruit, dry, cracked skin on his feet, and no response to a 10-g monofilament. Laboratory tests reveal an HbA1c of 9.8%, elevated total cholesterol, LDL, and triglycerides, low HDL, and various renal function abnormalities.
MANAGEMENT ISSUES AND OPTIONS

The major issue regarding the management of this patient is deciding which intervention to implement first. He clearly needs better glucose control, blood pressure control, correction of lipid abnormalities, lifestyle modification, eye care, renal care, and foot care now. He also needs to be screened for CVD.

Because this patient has clinical signs of significant insulin resistance—cardiovascular risk factors, a big belly, acanthosis nigricans and skin tags, and poor glucose control despite a high daily insulin dose—a C-peptide determination should be done to confirm that he is indeed insulin resistant.

Options to improve the patient’s glucose control include referring him to an endocrinologist or a certified diabetes educator, both of whom also can address his multiple diabetes-related problems, and adding metformin or a glitazone. Switching the type of insulin regimen is not likely to have much impact on glucose control, and increasing the insulin dose would probably require several daily injections.

Options to control the patient’s blood pressure include a 2-drug combination tablet—with 1 drug being an ACE inhibitor, ARB, or calcium channel blocker, and the other being a thiazide diuretic—and diet and exercise to lose weight. Referral to a nephrologist also seems prudent.

Options to improve his poor lipid profile include a mid-dose statin to lower his LDL to less than 70 mg/dL and the addition of lifestyle modification, fish oil, pioglitazone and/or metformin to increase his HDL and lower his triglycerides.

CASE DISPOSITION

A C-peptide determination revealed a level of 20 ng/mL, confirming extreme insulin resistance and explaining why this patient’s high insulin dose was having little effect on his insulin level and glucose control. He 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 brought his HbA1c levels into the 7.2% to 7.4% range. However, when he cannot exercise because of foot ulcers, his blood glucose levels increase.