Coronary Heart Disease in Type 2 Diabetes: The End Result of the Insulin Resistance Syndrome

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INSTRUCTIONS

JCOM CME The following article, "Coronary Heart Disease in Type 2 Diabetes: The End Result of the Insulin Resistance Syndrome," is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 60.

OBJECTIVES

JCOM CME After participating in the CME activity, primary care physicians should be able to:

1. Know the clinical features of the insulin resistance syndrome
2. Understand the role of insulin resistance in the pathogenesis of type 2 diabetes
3. Be familiar with the agents used in the management of patients with type 2 diabetes
4. Know the mechanisms known or postulated to contribute to the accelerated development of cardiovascular disease in the insulin resistance syndrome
5. Identify the pharmacologic agents used in the treatment of insulin resistance

INTRODUCTION

Diabetes mellitus affects over 16 million Americans and is increasing in prevalence as the population ages and becomes more obese and more sedentary. Approximately 90% of people with diabetes have type 2 diabetes, and the vast majority of these will die of cardiovascular disease. The purpose of this case presentation is to review the problem of cardiovascular disease in type 2 diabetes and to explore the role of the insulin resistance syndrome in its pathogenesis. Relevant modifiable risk factors and therapeutic interventions will also be reviewed.

CASE STUDY

Initial Presentation

A 43-year-old African American woman presents to her primary care physician with complaints of fatigue, frequent urination, and increased thirst over the past 3 or 4 months.

History

The patient states that she gets up to urinate 2 or 3 times every night and that she takes a nap whenever she gets the chance. She further reports that she has lost 10 lb over the past 2 months even though she was not dieting or exercising more than usual. She takes hydrochlorothiazide 25 mg daily for hypertension and has no known drug allergies. She had surgery to remove her gallbladder 5 years previously.

The patient is a teacher at a local elementary school. She has never smoked cigarettes and drinks ethanol only occasionally. She is married and has 2 children. Her father died of a heart attack at age 45, and her mother was diagnosed with diabetes at age 38. Her sister also has diabetes and weighs 210 lb. Her brother underwent coronary artery bypass surgery at age 41.

Physical Examination

Physical examination reveals a pleasant-appearing obese woman with a central distribution of obesity. She is 6'3" tall and weighs 225 lb (body mass index, 40 kg/m^2). Her blood pressure is 144/92 mm Hg and her heart rate is 70 bpm. She has patches of dark velvety skin in the creases of her neck and in her axillae (ie, acanthosis nigricans). Examination of the optic fundi reveals microaneurysms of the retina bilaterally. Cardiac examination reveals a regular rhythm without murmurs or gallops. Peripheral pulses are normal and the extremities are free of ulcerative lesions. The abdomen is obese, nontender, and free of hepatosplenomegaly. Neurologic examination reveals decreased vibratory sensation in both feet, but deep tendon reflexes are normal and sensation is intact to stimulation with a standard monofilament.

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Laboratory Findings

Laboratory studies reveal a normal blood count. Fasting plasma triglycerides are elevated at 215 mg/dL (reference range, 35 to 135 mg/dL), total cholesterol is 254 mg/dL, high-density lipoprotein (HDL) cholesterol is reduced at 36 mg/dL, and her calculated low-density lipoprotein (LDL) cholesterol is 174 mg/dL. Fasting plasma glucose is elevated at 146 mg/dL (reference range, 65 to 105 mg/dL). Hemoglobin A_{1c} (HbA_{1c}) is elevated at 9.6% (reference range, 4.4% to 6.5%). Serum chemistry, including electrolytes, BUN, creatinine, and liver function are normal, although serum uric acid is mildly elevated at 9.2 mg/dL (reference range, 2.5 to 6.5 mg/dL). Thyrotropin (TSH) levels are normal. Urine dipstick shows no evidence of gross proteinuria. An electrocardiogram is also normal.

Diagnosis and Initial Treatment

After confirming fasting hyperglycemia with a second determination of fasting plasma glucose (138 mg/dL), a diagnosis of type 2 diabetes is made. After discussing treatment options with the patient, a trial of lifestyle intervention is agreed upon.

The patient enrolls in a diabetes education class for specific instruction regarding diet and exercise. Given the patient's severe obesity, a reduced-calorie diet designed to induce a slow but steady weight loss is prescribed. Specifically, a moderate caloric restriction of 200 to 500 calories per day is recommended with additional instruction to reduce dietary protein to 10% to 20% of total calories and dietary fat to less than 30% of total calories, with no more than 10% of total calories to be derived from saturated fats. The remainder of the patient's daily caloric intake (50% to 60%) is to be derived from carbohydrates, with emphasis on high-fiber complex carbohydrates [1]. Furthermore, the patient is instructed to eat several small meals each day rather than a few large meals, since the practice of "nibbling" has been demonstrated to reduce plasma glucose and serum insulin concentrations in type 2 diabetes and to reduce LDL cholesterol levels [2]. Finally, the patient is instructed to increase her activity level by walking briskly for 30 to 40 minutes most days of the week [3].

- **What is the rationale for this management approach?**

Initial Treatment of Type 2 Diabetes

Most diabetes experts and textbooks recommend a trial of dietary therapy and lifestyle modification as the initial treatment for type 2 diabetes. Necessary components of lifestyle intervention include a reduced caloric intake, weight loss, adoption of a regular exercise routine, and elimination or reduction of known risk factors for cardiovascular disease (such as smoking). Lifestyle modification plays an important part in the management of diabetes and can lead to improved metabolic control [4]. Despite the fact that many patients will ultimately fail a trial of lifestyle modification, when successful, lifestyle modification is very rewarding to both the patient and the health care provider and can result in a marked improvement in overall health status. A trial of lifestyle modification also avoids the risks and costs of pharmacologic therapy and allows newly diagnosed patients to adapt to the large amount of new information they are receiving about their diabetes (such as learning to monitor their blood sugars and critically evaluate their diet).

Primary care physicians and diabetes educators should work together to achieve optimal treatment of type 2 diabetes. Studies have shown that a structured diabetes education that incorporates specific strategies to change behavior is most likely to improve clinical outcomes [4,5]. A routine of moderate physical activity (an average of 30 minutes per day) confers most of the cardiovascular benefits of more strenuous exercise and represents a sustainable activity for many patients. Long-term intervention with regular exercise has been shown to decrease insulin resistance and may delay development of diabetes in patients with impaired glucose tolerance. Exercise also improves the lipid profile, thereby decreasing the risk of cardiovascular disease. Diets high in cereal fiber, low in saturated fat, and with a low glycemic index are associated with improved glycemia and a reduced risk of coronary artery disease [6]. Garg et al [7] have demonstrated that in patients with type 2 diabetes, high-carbohydrate diets cause a persistent deterioration of glycemic control and accentuation of hyperinsulinemia compared with high–monounsaturated fat diets. These diets are also associated with increased plasma triglycerides and very-low-density lipoprotein (VLDL) cholesterol levels. Nevertheless, diets currently recommended by the American Diabetes Association advise that 50% to 60% of total calories be derived from carbohydrate in order to minimize intake of protein and fat. Reduction of total caloric intake and reliance on complex, high-fiber carbohydrates are components of the recommended diet for type 2 diabetes that are often overlooked, however.

Follow-up

The patient returns for follow-up 3 months later. She has gained 4 pounds despite the fact that she is "trying to exercise" and has been watching the amount of fat in her diet. She is monitoring her capillary blood glucose levels twice daily. Her fasting blood glucose levels are typically between 140 and 170 mg/dL, and occasional postprandial measurements have been between 225 and 250 mg/dL. Nocturia persists, and her HbA_{1c} remains elevated at 9.1%. Blood pressure is elevated at 155/95 mm Hg. A spot urine

Table 1. Clinical Features of the Insulin Resistance Syndrome

Clinical Feature	Role of Insulin Resistance
Glucose intolerance	Reduced glucose disposal in muscle in response to insulin results in hyperinsulinemia and, ultimately, pancreatic β-cell failure and hyperglycemia
Dyslipidemia	Insulin resistance in adipose tissue may cause increased delivery of fatty acids to the liver, resulting in increased VLDL production. Increased VLDL pool size results in increased transfer of cholesterol from HDL to VLDL, resulting in decreased HDL levels. Also, insulin resistance confers a state of relative deficiency of lipoprotein lipase activity.
Central obesity	A condition that is often present but not strictly necessary for the identification of the insulin resistance syndrome
Hypertension	Hyperinsulinemia increases renal sodium retention
Hyperuricemia	Hyperinsulinemia decreases urinary uric acid clearance

HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein. (Adapted with permission from Reaven GM. Insulin resistance and its consequences. In: LeRoith D, Taylor SI, Olefsky JM, editors. Diabetes mellitus: a fundamental and clinical text. 2nd ed. Philadelphia: Lippincott, Williams, and Wilkins; 2000:604–15.)

check reveals microalbuminuria with an albumin concentration of 66 mg/g creatinine (reference range, 30 mg/g). A repeat fasting lipid panel reveals elevated plasma triglycerides of 249 mg/dL, total cholesterol of 220 mg/dL, reduced HDL cholesterol of 33 mg/dL, and a calculated LDL cholesterol of 137 mg/dL.

After much discussion, she agrees to several changes in her medical regimen. Given the presence of diabetes and her strong family history for cardiovascular disease, her target LDL cholesterol level is less than 100 mg/dL [8]. She is started on simvastatin 20 mg daily. Due to concern over her uncontrolled hypertension, captopril 12.5 mg twice daily is added to the patient's hydrochlorothiazide. The captopril dose is gradually increased to 25 mg twice daily over the next several weeks, and her blood pressure stabilizes at approximately 125/80 mm Hg. Finally, glipizide GITS (a sulfonylurea) is started at 10 mg daily in an attempt to improve her glycemic control. The importance of diet and exercise is reaffirmed, and she is referred to a certified diabetes educator.

Three months later, the patient's HbA_{1c} is 7.9%. Her weight has increased by an additional 8 lb, but her blood pressure is controlled. Fasting triglycerides are 180 mg/dL and LDL cholesterol is 140 mg/dL.

- **What is the role of insulin resistance in the pathogenesis of type 2 diabetes?**

The Insulin Resistance Syndrome

The insulin resistance syndrome is typified by the existence of several associated pathophysiologic abnormalities in affected patients, including obesity, hypertension, dyslipidemia, hyperuricemia, and glucose intolerance [9]. All of these abnormalities are present in this patient. Overt diabetes is a late result of metabolic abnormalities that have been present for many years (even decades) in affected individuals, and early death due to cardiovascular disease is often the final result. The chronic, longstanding nature of the insulin resistance syndrome is emphasized by noting that the degree of insulin resistance is similar among patients with type 2 diabetes, patients with impaired glucose tolerance (or pre-diabetes), and nondiabetic first-degree relatives of patients with type 2 diabetes [10]. The presence of central obesity (ie, a waist-to-hip ratio greater than 0.85 in women or 1.0 in men) and acanthosis nigricans provides important clinical clues about the presence of the insulin resistance syndrome, and there is little need for a complex biochemical diagnostic investigation [11,12]. The presence of the insulin resistance syndrome in a nondiabetic patient is sometimes referred to as syndrome X, a label that reflects the complex and still poorly understood pathophysiology of the disorder. The prevalence of the insulin resistance syndrome is estimated to be 50% among hypertensive patients, and overt diabetes affects 1 in every 18 Americans [13–15]. The clinical features of the insulin resistance syndrome are summarized in **Table 1**.

Insulin resistance is primarily an impaired metabolic response to insulin [16]. Affected patients typically exhibit higher insulin levels than would normally be appropriate for a given plasma glucose concentration [13,14,17]. In the clinical setting, however, it is rarely necessary to measure plasma insulin levels because insulin secretory capacity varies according to the severity and duration of the underlying metabolic disorder and because randomly obtained insulin concentrations are a poor indicator of insulin resistance or sensitivity. Aside from its association with disordered glucose homeostasis, the presence of insulin resistance is also reflected in the other biological functions of insulin, such as its effects on vascular endothelium, lipid and protein metabolism, and fibrinolysis [16,17]. A complete understanding of mechanisms responsible for this syndrome is not currently known. It is generally accepted, however, that postreceptor signaling defects contribute significantly to insulin resistance [18,19].

Other Pathogenetic Factors

Aside from insulin resistance, other aspects of the pathogenesis of type 2 diabetes deserve mention. Specifically, impaired suppression of endogenous hepatic glucose production by insulin is an early and distinct metabolic error in

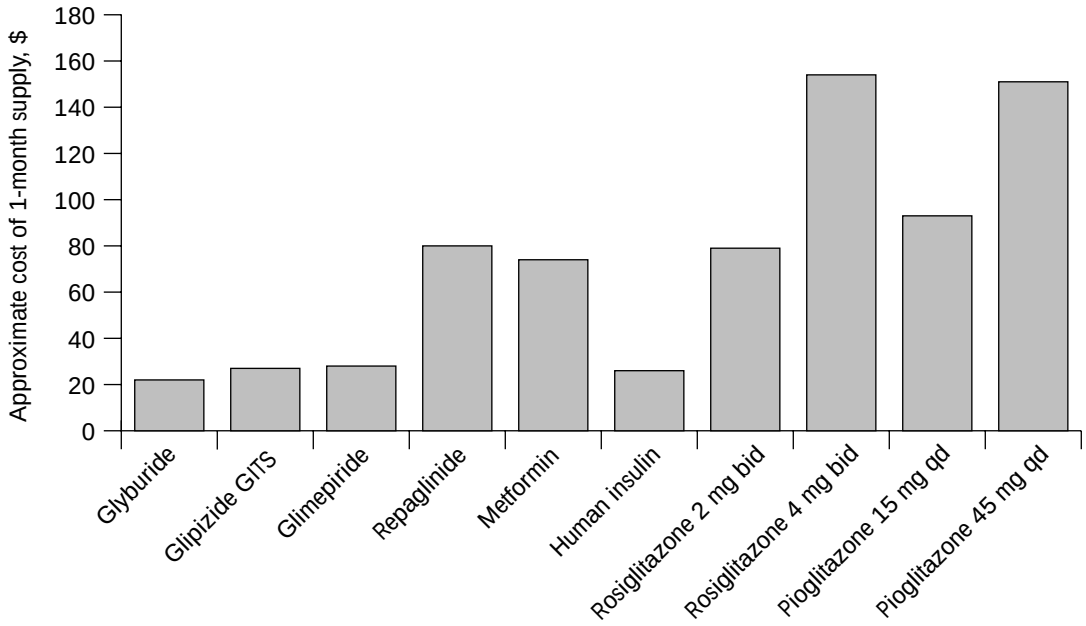

Figure 1. Approximate retail cost of a 1-month supply of a medium-sized dose of various diabetes medications (based on telephone query to Walgreens, October 2000).

type 2 diabetes [20]. This defect is perhaps most easily understood as "insulin resistance of the liver" and is the metabolic error most directly targeted by metformin. Increased fasting glucose production resulting from inappropriately robust rates of gluconeogenesis is the basis for fasting hyperglycemia in type 2 diabetes [21]. A third metabolic defect in type 2 diabetes is failure of the pancreatic β-cells to secrete adequate amounts of insulin to prevent hyperglycemia after a glucose load [22]. Although this defect is present in essentially all patients with type 2 diabetes, it is also true that absolute insulin concentrations may be markedly elevated compared to nondiabetic subjects after a glucose challenge, especially early in the clinical course of the disease [23]. The presence of underlying resistance to the action of insulin in peripheral tissues, however, ensures that even greatly elevated levels of insulin are inadequate to maintain normal glucose homeostasis. Impaired β–cell function is the target of drugs that increase endogenous insulin secretion, such as the sulfonylureas and meglitinides.

- **What is the approach to pharmacologic therapy in the insulin-resistant patient with type 2 diabetes?**

Pharmacologic Therapy in Type 2 Diabetes

Regarding the choice of pharmacologic therapy in patients with newly diagnosed type 2 diabetes, physicians are currently faced with more options than ever before, and excellent reviews of this topic currently exist [24]. Indeed, therapeutic agents are available that address all of the known pathogenetic factors in type 2 diabetes: impaired β-cell function (sulfonylureas, meglitinides, insulin), inappropriate hepatic glucose production (biguanides), obesity (intestinal lipase inhibitors, appetite suppressants), and peripheral insulin resistance (thiazolidinediones). As a result, achievement of target glycemic goals is now a realistic possibility for most patients with the disease. There is not, however, a consensus on how these agents should be used in any given patient or, for that matter, in what order they should be used. Nevertheless, there are many criteria that can potentially be applied to assist in this choice. For example, if one strongly believes that treating the underlying insulin resistance is of paramount importance in type 2 diabetes, then thiazolidinediones would be a logical choice for most patients. To date, however, no single class of agents has been demonstrated to be clearly superior to the others with respect to either indices of glycemic control or other clinically relevant outcomes in type 2 diabetes. In various studies, all of the available oral diabetes agents have been shown to cause approximately a 0.5% to 1% reduction in HbA_{1c} as compared with placebo when used as monotherapy. **Figure 1** shows the approximate retail cost of a 1-month supply of each of the drugs based upon a query to a leading national drugstore chain. In the absence of a demonstrable superiority of any single agent in relevant health-related outcomes in type 2 diabetes, cost represents a

Table 2. Summary of Various Combination Therapy Strategies in Type 2 Diabetes

Combination Therapy Regimen	Approximate Efficacy*	Reference
Sulfonylurea + metformin	0.5 – 1%	29
Sulfonylurea + thiazolidinedione	0.5 – 1.5%	30
Metformin + thiazolidinedione	1%	31
Metformin + insulin	0.5 – 1%	32,33
Thiazolidinedione + insulin	0.5 – 1%	34,35

*Approximate reduction in HbA_{1c} relative to placebo.

logical criterion to apply to the choice of therapy in affected individuals. As a result, this patient was started on a course of sulfonylurea monotherapy with the expectation of a 1% to 2% reduction in HbA_{1c} over the next several weeks.

Attainment of target LDL cholesterol levels (ie, < 100 mg/dL) is of critical importance in patients with the insulin resistance syndrome. Several studies have now established that patients with type 2 diabetes respond to therapy with HMG-CoA reductase inhibitors (statins) and that cardiovascular outcomes such as death and nonfatal myocardial infarction are improved. As such, these agents are the drugs of choice for treating the dyslipidemia associated with the insulin resistance syndrome. At high doses, certain statins (including simvastatin and atorvastain) will also reduce hypertriglyceridemia.

Microalbuminuria has long been appreciated to be a strong predictor of future cardiovascular events in individuals with type 2 diabetes. The nature of this association is not fully understood, but it is probable that microalbuminuria reflects subtle underlying abnormalities of glomerular anatomy and secondary activation of the renin-angiotensin system. Chronic activation of the renin-angiotensin system, in turn, probably has a number of adverse effects on cardiovascular physiology that favors the development of ischemic coronary artery disease. These include systemic vasoconstriction, vascular smooth muscle cell proliferation, hypertension, ventricular hypertrophy, and impaired fibrinolysis. Angiotensin-converting enzyme (ACE) inhibitors directly address this problem by preventing angiotensin II production and by reducing afterload stress on the heart. As such, ACE inhibitors have been shown to improve survival and reduce cardiovascular events in patients with pre-existent ischemic cardiomyopathy [25]. Whether or not these drugs confer similar benefit to diabetes patients without ventricular dysfunction or hypertension was unknown until the recent conclusion of the Heart Outcomes Prevention Evaluation (HOPE) study [26]. This study demonstrated that ACE inhibitor therapy reduced the risk of death and of myocardial infarction among 9297 high-risk patients without known ventricular dysfunction (including 3577 patients with diabetes) by 22%. As such, these agents are the current drugs of choice for treating hypertension in patients with type 2 diabetes. Although it is not yet standard therapy to treat diabetes patients without hypertension with ACE inhibitors as a preventive measure, it seems likely that this mode of therapy will become standard in the future.

One Year Later

One year later, the patient returns and reports that her glucose control has deteriorated. Her HbA_{1c} level is 9.4%. She insists that she is maintaining her diet. She has not gained any additional weight. Metformin 500 mg twice daily is added to her regimen and her HbA_{1c} level subsequently decreases to 8.1%.

- **What is the appropriate response to secondary sulfonylurea failure?**

Responding to Deteriorating Control

The United Kingdom Prospective Diabetes Study (UKPDS) clearly demonstrated that the natural history of type 2 diabetes is a steady, relentless worsening of metabolic control over time [27]. As such, once-effective monotherapies typically become insufficient to achieve target glycemic goals (a phenomenon termed "secondary failure") [27]. This is likely due to decreasing β-cell function and/or increasing insulin resistance. Results from the UKPDS suggest that the progressive failure of sulfonylurea and metformin monotherapy is most consistent with β-cell failure over the course of a 9-year observation period. In that study, 50% of patients on monotherapy required the addition of another pharmacologic agent to maintain glycemic control within 3 years of starting monotherapy [27,28]. Thus, most patients with type 2 diabetes will ultimately require combination therapy to achieve target glycemic goals [27]. Physicians must watch carefully for a sustained deterioration in glycemic control and be aggressive in accelerating diabetes therapy when such a deterioration occurs. **Table 2** summarizes the efficacy of various combination therapies relative to monotherapy. Metformin was added to sulfonylurea therapy in this patient because of its relatively low cost. Although metformin monotherapy usually does not cause additional weight gain, this is not the case when metformin is combined with sulfonylurea. One recent study, however, has demonstrated that insulin plus metformin results in substantial improvements in glycemic control without the additional weight gain observed with sulfonylurea plus insulin, insulin plus sulfonylurea and metformin, or insulin alone [29].

Additional Follow-up

Over the course of the next few years, the patient's glucose control slowly worsens despite increasing doses of metformin and glipizide GITS. As such, a single injection of NPH insulin at bedtime is eventually added to her regimen in an attempt to normalize fasting glucose concentrations. At the age of 51, the patient is identified as being perimenopausal, and hormone replacement therapy is initiated. She subsequently begins to experience episodes of mild chest discomfort during exertion, which she ignores. She finally presents to a local emergency room after a more a severe episode of chest pain. An electrocardiogram shows evidence of anterior wall ischemia, and subsequent coronary artery angiography reveals a 75% proximal stenosis of her left anterior descending artery. The lesion is treated with balloon angioplasty, and her symptoms abate.

Shortly thereafter, laboratory studies reveal a fasting plasma glucose concentration of 186 mg/dL and a HbA_{1c} level of 9.8%. Serum creatinine is 1.2 mg/dL, and a fasting lipid panel reveals triglycerides of 240 mg/dL, total cholesterol of 258 mg/dL, HDL cholesterol of 32 mg/dL, and LDL cholesterol of 152 mg/dL on simvastatin 20 mg daily. Liver function tests, complete blood counts, and TSH results are within normal limits.

- **What accounts for this patient's premature coronary artery disease?**

Cardiovascular Disease and the Insulin Resistance Syndrome

Patients with type 2 diabetes often develop premature coronary artery disease and often have coronary artery disease on presentation. Furthermore, atherosclerosis is closely linked to the associated metabolic abnormalities of the insulin resistance syndrome, but the genesis of this clinical problem is almost certainly multifactorial [36,37]. In fact, the severity of hyperglycemia and dyslipidemia present in patients with type 2 diabetes is inadequate to explain the marked increase in cardiovascular disease that occurs in affected patients. Thus, the confluence of risk factors present in this patient (both known and unknown), combined with the imperfect state of modern medical therapy, ultimately resulted in cardiovascular disease in this case. Mechanisms known or postulated to explain the accelerated development of atherosclerotic disease in the insulin resistance syndrome are discussed below.

Dyslipidemia

Although LDL cholesterol concentrations in type 2 diabetes do not differ from those of the nondiabetic population, abnormalities of circulating lipids have been identified that promote atherogenesis in type 2 diabetes. Specifically, VLDL cholesterol particles tend to be cholesterol-enriched, HDL cholesterol levels tend to be suppressed, and LDL particles tend to be smaller and denser. Smaller and denser LDL particles may be more susceptible to oxidative modification and are more prone to being sequestered by endothelium-associated macrophages, a process known as foam cell formation [38–41]. Hyperinsulinemia itself may promote atherosclerosis by stimulating inhibitors of fibrinolysis in arterial tissues and by inducing proliferation and growth of arterial smooth muscle cells [38,42]. Increased free fatty acid levels associated with insulin resistance leads to endothelial dysfunction.

Hypertension

Studies have shown that plasma insulin levels are increased in both treated and untreated patients with essential hypertension [43,44]. Several mechanisms may be involved in the hypertension observed in the insulin resistance syndrome. Insulin-resistant patients may have increased responsiveness to angiotensin [45]. Increased sympathetic activity may be present and increased plasma levels of norepinephrine have been reported [44]. Endothelial dysfunction and impaired smooth muscle relaxation may also play a role in the pathogenesis of hypertension in patients with the insulin resistance syndrome [46]. Insulin-mediated retention of sodium and fluid has also been implicated as a cause of hypertension in insulin-resistant individuals [43].

Glucose Intolerance and Diabetes

As mentioned previously, diabetes is a late manifestation of the insulin resistance syndrome. **Figure 2** shows a schematic of the natural history of the insulin resistance syndrome. Interestingly, patients with impaired glucose tolerance (or pre-diabetes) possess the same high risk for accelerated cardiovascular disease as do those with overt diabetes (ie, a two- to fourfold increase in risk compared to nondiabetic individuals) [47]. By the time diabetes is diagnosed, a large proportion of patients already have evidence of clinically significant vascular damage.

Endothelial Dysfunction

Endothelial dysfunction plays an important role in the pathogenesis of atherosclerosis. The endothelium is a metabolically active tissue and plays a vital role in regulating vascular smooth muscle tone [48]. Insulin plays an important role in vascular smooth muscle relaxation through its partial mediation of endothelium-derived nitric oxide release [46]. This effect of insulin is diminished in insulin-resistant patients. Impairment of nitric oxide–mediated relaxation of the coronary arteries may be one mechanism for the formation of flow-limiting lesions and small-vessel disease observed in many patients with diabetes.

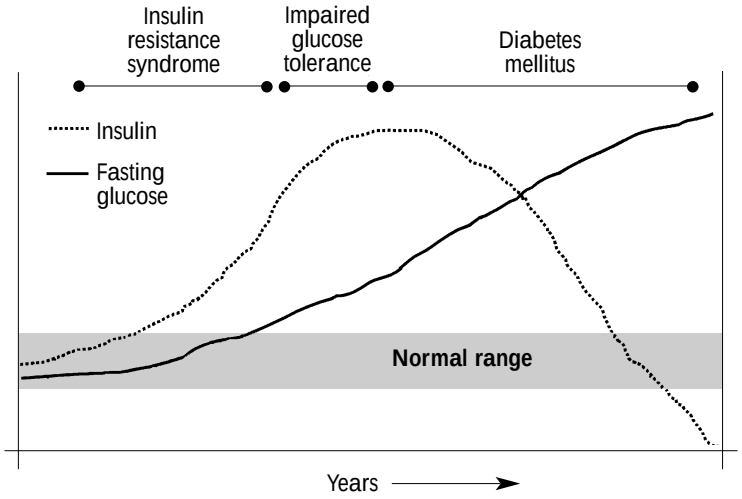

Figure 2. Schematic representation of the natural history of the insulin resistance syndrome during an idealized lifetime. Underlying insulin resistance begets hyperinsulinemia. As β-cell failure begins to develop, impaired glucose intolerance and, finally, overt diabetes mellitus ensues.

Coagulation Abnormalities

Insulin has varied effects on components of the coagulation system that may adversely affect cardiovascular outcome. Plasminogen activator inhibitor 1 (PAI-1) is the primary inhibitor of endogenous fibrinolysis, and elevated levels of PAI-1 have been associated with an increased risk of myocardial infarction [49,50]. Both insulin and proinsulin are known to increase synthesis of PAI-1 [51]. Furthermore, levels of fibrinogen and von Willebrand's factor are increased in diabetes and may contribute to a relatively prothrombotic state [52].

Nontraditional Risk Factors

One recent study documented that numerous nontraditional risk factors are independently associated with cardiovascular disease in type 2 diabetes after correcting for traditional risk factors, including decreased serum albumin concentrations, increased fibrinogen levels, increased factor VIII levels, increased von Willebrand's factor levels, and increased total leukocyte count [53]. This information raises new questions about the pathogenesis of cardiovascular disease in type 2 diabetes and suggests that inflammation and/or vascular injury may play a greater role in its development than previously appreciated. Indeed, these factors may prove to be unrelated to insulin resistance. Nevertheless, these new risk factors are primarily of interest to researchers at the present time, and clinical interventions targeting them (or the vascular pathology they reflect) have yet to be performed and have not been yet been demonstrated to reduce the occurrence of cardiovascular disease in type 2 diabetes.

- **Can pharmacologic therapy alter the natural history of the insulin resistance syndrome?**

There are currently 2 classes of drugs that are effective in the treatment of insulin resistance. The first of these is the biguanides, a class of drugs that presently includes only metformin. Metformin has effects mainly on the liver and acts to decrease hepatic glucose production [54,55]. In the UKPDS, patients randomized to metformin had a significant decrease in cardiovascular events; however, assignment to study groups was not strictly adhered to in this study so these results are difficult to interpret. The other class of drugs that targets insulin resistance is the thiazolidinediones; this class presently includes rosiglitazone and pioglitazone. These drugs reduce insulin resistance and increase insulin-mediated glucose disposal in skeletal muscle through their activation of the peroxisome proliferator activator receptor gamma (PPARγ) system. They confer additional potential benefit by improving several metabolic abnormalities associated with the insulin resistance syndrome [56,57]. Troglitazone (the prototype thiazolidinedione that is no longer commercially available) has been shown to decrease PAI-1 levels, and all of the thiazolidinediones decrease free fatty acid levels [57–59]. Reduced fatty acidemia may, in turn, lead to an improvement in endothelial function. Both rosiglitazone and pioglitazone have been shown to be effective in reducing HbA_{1c} and fasting blood glucose. In addition, pioglitazone has been shown to reduce plasma triglyceride levels, while the effect of rosiglitazone on triglycerides has been variable [60,61]. Although the thiazolidinediones may eventually be shown to prevent cardiovascular disease in patients with insulin resistance, no controlled clinical trials have yet demonstrated an improvement in clinically important cardiovascular outcomes with the thiazolidinediones, so the question of whether or not the natural history of the insulin resistance syndrome can be modified through the use of these drugs remains unanswered. Since the thiazolidinediones address insulin resistance through a different

mechanism of action compared with metformin, however, the combination of a thiazolidinedione and metformin is an appropriate one to use in response to the failure of metformin monotherapy or combination therapy [31].

Further Pharmacologic Intervention

Pioglitazone 15 mg daily is added to the patient's regimen, and the dose was subsequently increased to 30 mg daily. Because of a significant decrease in her blood glucose, she is able to discontinue insulin injections. At present, the patient's HbA_{1c} level is 7.2% on a regimen of glipizide GITS 10 mg daily, metformin 1000 mg twice daily, and pioglitazone 30 mg daily. She is trying to increase the frequency of her exercise and further reduce her weight. Her fasting lipid panel shows a total cholesterol of 179 mg/dL, triglycerides of 162 mg/dL, HDL cholesterol of 46 mg/dL, and LDL cholesterol of 99 mg/dL on simvastatin 80 mg daily. Her blood pressure and microalbuminuria are stable on lisinopril 40 mg and hydrochlorothiazide 25 mg daily, and she has had no further episodes of chest pain.

SUMMARY

This case highlights the classical features of the insulin resistance syndrome and its final metabolic manifestation as type 2 diabetes. The burden of cardiovascular morbidity and mortality associated with this syndrome represents a huge concern for health care policy makers and a difficult clinical challenge for practicing physicians. Nevertheless, each metabolic disturbance of this syndrome deserves careful attention and, often, specific pharmacologic therapy. Goal-directed therapy to normalize blood glucose concentrations, blood pressure, body weight, and LDL cholesterol levels offers affected patients the best chance for avoiding the fearsome cardiovascular ramifications of this syndrome. Physicians must remain aware of the optimal clinical indications for these drugs and also be mindful of their limitations. The number of options available for treatment of the insulin resistance syndrome will only become larger in the future, and it seems likely that the threat of cardiovascular disease will become increasingly manageable with new and effective therapies.

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JCOM CME

EVALUATION FORM: Coronary Heart Disease in Type 2 Diabetes: The End Result of the Insulin Resistance Syndrome

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Part 1. Please respond to each statement.

	Strongly Agree				Strongly Disagree
	5	4	3	2	1
I was provided with new information pertinent to my practice	❑	❑	❑	❑	❑
I reaffirmed a specific skill or knowledge.	❑	❑	❑	❑	❑
This article will help with clinical decision making.	❑	❑	❑	❑	❑
Relevant clinical outcomes are addressed.	❑	❑	❑	❑	❑
The case is communicated in a manner that kept my interest.	❑	❑	❑	❑	❑
The case presentation is realistic and effective.	❑	❑	❑	❑	❑
I could easily interpret the tables and figures.	❑	❑	❑	❑	❑
My attitude about this topic changed in some way.	❑	❑	❑	❑	❑

Additional comments: _____

_____

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

❑ see no need to change my practice.

❑ will seek more information before modifying my practice.

❑ intend to change the following aspect(s) of my practice: (Briefly describe)

_____

_____

Part 3. Statement of completion: I attest to having completed the CME activity.

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