**ABSTRACT**

The link between type 2 diabetes and cardiovascular disease has been amply demonstrated in numerous studies. People with diabetes have a higher risk for cardiovascular events and higher mortality rates from cardiovascular causes than people who do not have diabetes. However, diabetes develops over time, preceded by several years of gradually worsening insulin resistance. Ideally, persons at risk for diabetes should be identified at this time, when strategies to prevent type 2 diabetes and its cardiovascular complications are most likely to be successful. This article reviews the evidence linking diabetes to cardiovascular disease, discusses the role of insulin resistance and hyperinsulinemia in the progression from normoglycemia to diabetes, and explores the association of insulin resistance, diabetes, and cardiovascular risk. It also addresses why normalization of glucose, blood pressure, and lipid levels is crucial in the prevention of or delaying the progression to diabetes and cardiovascular disease.


**IMPACT OF ATHEROSCLEROSIS AND DIABETES**

Historically, diabetes has been considered a blood glucose disease with hyperglycemia as its cardinal symptom. However, considerable evidence indicates that diabetes is also a cardiovascular disease in which hyperglycemia is a symptom, but not the underlying issue. Because both diabetes and cardiovascular disease develop over the course of years, nurse practitioners, physician assistants, and other healthcare professionals involved in primary care are in an excellent position to detect these diseases in their early stages and prevent or delay disease progression.

**THE LINK BETWEEN TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE**

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which examined the incidence of fatal and nonfatal myocardial infarction (MI) over 7 years in 1059 patients with diabetes and 1373 nondiabetic patients. The study found that the chance of having an MI over 7 years was 1 in 30 among patients without diabetes and no prior history of MI, but 1 in 5 with a previous MI. By comparison, the chance was slightly higher than 1 in 5 among patients with diabetes but no prior MI, and 1 in 2, or 50%, in those with diabetes and a previous MI. Moreover, the risk was slightly higher than 50% in women with diabetes who had previously had an MI.

Aside from increasing the risk for a cardiovascular event, diabetes has a considerable impact on overall health and survival. Largely because of its chronic complications, including atherosclerosis, diabetes is the seventh leading cause of death in the United States, and accounts for more deaths annually than breast cancer or AIDS. Diabetes also decreases life expectancy by 15 years. Moreover, Census Bureau data indicate that Caucasian children born in the year 2000 have a 1 in 3 chance of developing diabetes in adulthood, whereas children in high-risk ethnic groups—African American, Native American, Asian American, Pacific Islander, and Hispanic American—have a 50% risk.

Against this backdrop, clinicians must keep diabetes risk in mind in all patients, especially those at risk for cardiovascular disease or those with a history of a cardiac event. These patients require further evaluation and then appropriate intervention or referral.

**PATHOPHYSIOLOGY OF TYPE 2 DIABETES**

The pathophysiology of type 2 diabetes involves 3 major underlying defects that help to explain how prediabetes progresses to diabetes and how diabetes increases the risk for cardiovascular disease: insulin resistance, increased hepatic glucose output, and decreased pancreatic insulin secretion.

**INSULIN RESISTANCE**

Insulin resistance, which is present in approximately 92% of people with type 2 diabetes, is a defect in insulin utilization that precedes the manifestations of type 2 diabetes, often by 5 to 10 years or more. 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 by poor insulin utilization, resulting in a significant increase in insulin-mediated glucose uptake and mildly elevated glucose levels. The pancreas, which “works” at approximately 5% of its capacity to maintain glucose homeostasis in normal individuals, responds to the rise in blood glucose by providing increased insulin, resulting in hyperinsulinemia and normoglycemia. Over time, the insulin resistance progresses and 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 prediabetic state. Insulin production begins to drop off and blood glucose levels increase, eventually leading to diabetes. 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 insulin resistance and impaired glucose tolerance to diabetes, are shown in Figure 1. In years past, most cases of diabetes were diagnosed when glucose levels had been elevated for several years. Although more people are now identified
at earlier stages along the spectrum, the goal is to intervene with preventive measures 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. Moreover, a study investigating hyperinsulinemia in men found that a high fasting insulin level was an independent predictor of ischemic heart disease, regardless of lipid levels, smoking, and hypertension. Clinical markers of hyperinsulinemia include high triglyceride and low high-density lipoprotein cholesterol levels, elevated blood pressure, and central obesity. These markers can be used to identify which patients to target for early treatment of insulin resistance and prevention of type 2 diabetes.

**Increased Hepatic Glucose Output**

A second defect underlying type 2 diabetes is increased hepatic glucose output, which results in increased glycogen production and gluconeogenesis, and fasting hyperglycemia due to 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**

The third defect underlying type 2 diabetes is decreased secretion of insulin from the pancreas. Prior to the onset of diabetes, the pancreas increases insulin output to maintain normoglycemia. Eventually, the pancreas can no longer continue producing such high amounts of insulin and, as insulin levels begin to decrease, glucose levels start 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**

In addition to being a coronary artery disease risk equivalent, diabetes is associated with several well-recognized risk factors for cardiovascular disease, including lipid abnormalities and hypertension. However, insulin resistance is also associated with a number of risk factors for cardiovascular disease (Table), including the highly atherogenic form of small, dense, low-density lipoprotein (LDL) cholesterol known as Pattern B. Although elevated levels of LDL cholesterol in any patient increase the risk for

### Table. Cardiovascular Risk Factors Associated with Insulin Resistance

- Elevated blood pressure
- Hyperinsulinemia
- Low HDL cholesterol levels
- Elevated triglyceride levels
- Small, dense LDL cholesterol particles
- Increased apolipoprotein B levels
- Endothelial dysfunction
- Increased fibrinogen levels
- Increased levels of plasminogen activator inhibitor-1
- Increased levels of C-reactive protein and other inflammatory markers
- Increased blood viscosity
- Microalbuminuria

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Data from McFarlane et al. J Clin Endocrinol Metab. 2001;86:713-718.

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**Figure 2. Association of Insulin Resistance, Type 2 Diabetes, and Cardiovascular Disease**

HDL-C = high-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor-1; S, D LDL = small, dense low-density lipoprotein; TG = triglycerides.

The association of insulin resistance, type 2 diabetes, and cardiovascular disease is illustrated in Figure 2. Insulin resistance is present well before the manifestations of type 2 diabetes appear. Insulin resistance and its resultant hyperinsulinemia are the first steps of the process, and they continue to be present throughout the progression from normoglycemia to type 2 diabetes.

A timeline of the natural history of the progression of prediabetes to type 2 diabetes is shown in Figure 3. 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. Importantly, the onset of macrovascular complications may occur even earlier. Thus, it is important to assess patients for diabetes and its precursors early in order to try to prevent these chronic complications from occurring.

**IMPACT OF DIABETES AND MULTIPLE RISK FACTORS**

As demonstrated in the Nurses’ Health Study, which followed more than 117,000 women for 20 years, both diabetes and prediabetes significantly increased the risk of cardiovascular disease. Compared to women who did not develop diabetes during the study (relative risk = 1), those who did develop diabetes were at substantially higher risk to suffer an MI or stroke. The relative risk was 2.82 prior to the diagnosis, 3.71 after the diagnosis of diabetes, and 5.02 if diabetes was present at baseline.

Similarly, the Multiple Risk Factor Intervention Trial, which followed nearly 348,000 men for an average of 12 years, demonstrated that the presence of elevated total cholesterol, hypertension, and/or smoking increased the risk of death from a cardiovascular cause in people with and without diabetes. Although death rates rose in people without diabetes with the addition of each of the 3 risk factors, the increases were even more pronounced in those with diabetes. Death rates were 2 times higher in people with diabetes who had 1 risk factor than in those who had none of the 3 risk factors, 3 times as high in people with diabetes who had 2 risk factors, and 4 times higher in people with diabetes who had all 3 of the risk factors.

The findings of both studies underscore the impact of diabetes on cardiovascular risk and the need for aggressive intervention to reduce their cardiovascular risk factors.

**TREATING DIABETES AND PREDIABETES**

Treatment of individuals with prediabetes and those with type 2 diabetes requires intervention to reduce risk factors that contribute to diabetes and cardiovascular disease. Motivating patients to change dietary habits, develop a regular exercise program, and maintain an optimal weight are our first priority. Even small changes in diet, a modest increase in exercise or physical activity, or weight loss can be significant in lowering glucose and blood pressure and normalizing lipid levels. Three interventional trials have shown that patients randomized to intensive lifestyle intervention had a significantly reduced risk of developing type 2 diabetes. Drug 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 aspirin each day to lower their risk for cardiovascular disease.

![Figure 3. Natural History of the Progression of Prediabetes to Type 2 Diabetes](image-url)
CONCLUSIONS

Diabetes is not merely a blood glucose disease, but a cardiovascular disease in which hyperglycemia is a symptom. Indeed, the influence of diabetes on cardiovascular disease is considerable, with studies showing a higher incidence of cardiovascular events and increased mortality from cardiovascular causes in persons with diabetes.

Diabetes develops over time, as does cardiovascular disease, thus affording healthcare professionals the opportunity to intervene with appropriate preventive measures. Diabetes, for example, is preceded by insulin resistance and hyperinsulinemia, both of which are associated with cardiovascular risk factors such as obesity, hypertension, lipid abnormalities, and endothelial dysfunction. Without intervention, insulin resistance progresses to impaired glucose tolerance and type 2 diabetes, which further increases the risk for cardiovascular disease.

The goal is to identify people at risk before they develop diabetes and to help them normalize their glucose, blood pressure, and lipid levels. Weight loss, lifestyle modification, and reduction of cardiovascular risk factors are keys to intervention.

REFERENCES