

In Brief

The pathophysiology of the link between diabetes and cardiovascular disease (CVD) is complex and multifactorial. Understanding these profound mechanisms of disease can help clinicians identify and treat CVD in patients with diabetes, as well as help patients prevent these potentially devastating complications. This article reviews the biological basis of the link between diabetes and CVD, from defects in the vasculature to the cellular and molecular mechanisms specific to insulin-resistant states and hyperglycemia. It concludes with a discussion of heart failure in diabetes, a clinical entity that demonstrates many of the mechanisms discussed.

The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids

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Diabetes is a prime risk factor for cardiovascular disease (CVD). Vascular disorders include retinopathy and nephropathy, peripheral vascular disease (PVD), stroke, and coronary artery disease (CAD). Diabetes also affects the heart muscle, causing both systolic and diastolic heart failure. The etiology of this excess cardiovascular morbidity and mortality is not completely clear. Evidence suggests that although hyperglycemia, the hallmark of diabetes, contributes to myocardial damage after ischemic events, it is clearly not the only factor, because both pre-diabetes and the presence of the metabolic syndrome, even in normoglycemic patients, increase the risk of most types of CVD.¹⁻⁴

In 2002, a survey of people in the United States with diagnosed diabetes found that, surprisingly, 68% of patients did not consider themselves at risk for heart attack or stroke.⁵ In addition, only about half of patients surveyed reported that their health care providers discussed the high risk of CVD in diabetes and what steps they could take to reduce that risk.⁵ Fortunately, we are now making the link. Health care providers are now focused on decreasing cardiovascular risk in patients with diabetes by treating dyslipidemia and hypertension and by improving glycemic control.⁶ Moreover, the American Diabetes Association/American College of Cardiology “Make the Link” public awareness campaign has improved

knowledge related to CVD in patients with diabetes.

However, managing cardiovascular risk factors in patients with diabetes does not eradicate these complications. We are only just beginning to understand the complex and multifactorial etiology of CVD in diabetes. This review will attempt to provide an explanation of the current scientific knowledge in this field, from defects in the large blood vessels (macrovasculature) and the small blood vessels (microvasculature) to the less well-understood cellular and molecular mechanisms of CVD in patients with diabetes.

Macrovasculature

Atherosclerosis is the major threat to the macrovasculature for patients with and without diabetes. The general pathogenesis of atherosclerosis has been reviewed elsewhere,⁷ but several factors specific to diabetes are worth mentioning here. Clinically, dyslipidemia is highly correlated with atherosclerosis, and up to 97% of patients with diabetes are dyslipidemic.⁸ In addition to the characteristic pattern of increased triglycerides and decreased HDL cholesterol found in the plasma of patients with diabetes, abnormalities are seen in the structure of the lipoprotein particles. In diabetes, the predominant form of LDL cholesterol is the small, dense form. Small LDL particles are more atherogenic than large LDL particles because they can more easily penetrate and form stronger attachments to the arterial

wall, and they are more susceptible to oxidation. Because less cholesterol is carried in the core of small LDL particles than in the core of large particles, subjects with predominantly small LDL particles have higher numbers of particles at comparable LDL cholesterol levels.⁹

Oxidized LDL is pro-atherogenic because once the particles become oxidized they acquire new properties that are recognized by the immune system as “foreign.” Thus, oxidized LDL produces several abnormal biological responses, such as attracting leukocytes to the intima of the vessel, improving the ability of the leukocytes to ingest lipids and differentiate into foam cells, and stimulating the proliferation of leukocytes, endothelial cells, and smooth muscle cells,¹⁰ all of which are steps in the formation of atherosclerotic plaque. In patients with diabetes, LDL particles can also become glycated, in a process similar to the glycation of the protein hemoglobin (measured in the hemoglobin A_{1c} [A1C] assay). Glycation of LDL lengthens its half-life¹¹ and therefore increases the ability of the LDL to promote atherogenesis. Paradoxically, however, glycation of HDL shortens its half-life and renders it less protective against atherosclerosis.¹²

Moreover, diabetic blood is more likely to be high in triglycerides. Hypertriglyceridemia in diabetes occurs, in part, because insulin action regulates lipid flux. Insulin promotes the activity of the enzyme lipoprotein lipase, which mediates free fatty acid uptake into adipose tissue (storage) and also suppresses the activity of the enzyme hormone-sensitive lipase, resulting in decreased release of free fatty acids into the circulation.¹³ Hypertriglyceridemia can lead to increased production of the small, dense form of LDL and to decreased HDL transport of cholesterol back to the liver.¹⁴

Dyslipidemia is only one mechanism by which diabetes promotes atherosclerosis; endothelial dysfunction often contributes. Healthy endothelium regulates blood vessel tone, platelet activation, leukocyte adhesion, thrombogenesis, and inflammation. The net effect of healthy endothelium is vasodilatory, anti-atherogenic, and anti-inflammatory.¹⁵ When these mechanisms are defective, the process of atherosclerosis is accelerated. Therefore, both insulin

deficiency and insulin resistance promote dyslipidemia accompanied by increased oxidation, glycosylation, and triglyceride enrichment of lipoproteins. In addition, endothelial dysfunction is present, and all of these factors contribute to the increase in atherogenicity, and thus macrovascular disease, found in patients with diabetes.

Microvascular Disease

Typically, when we hear the term “microvascular disease” associated with diabetes, we think of retinopathy, nephropathy, and neuropathy. In addition, however, small vessels throughout the body are affected by diabetes, including those in the brain, heart, and peripheral vasculature. This small vessel damage is typically not related to atherosclerosis and is not predicted by lipid levels. Whereas atherosclerosis is the major threat to the macrovasculature, a variety of cellular and molecular mechanisms contribute to microvascular disease in diabetes.

The microcirculation is regulated by central and local regulatory mechanisms. The central regulation is via autonomic sympathetic and parasympathetic nerves that reach the vascular smooth muscle. Local regulation is carried out by substances produced by the endothelial cells and by local products of metabolism. The endothelium produces both vasodilators and vasoconstrictors. Normally, the vascular smooth muscle receives continuous regulatory nerve signals and a continual supply of vasodilating nitric oxide (NO) from the endothelium, as well as a continuous flow of metabolic products. These regulatory mechanisms adjust microvascular flow instantaneously to meet the metabolic needs of the tissue.¹⁶

Diabetes contributes to defects in the autonomic nervous system, the endothelium, and local metabolism, all of which can result in microvascular disease. Diabetic autonomic neuropathy (DAN) is one factor associated with impaired autoregulation of blood flow in a variety of vascular beds, including the skin and the heart.^{17,18} Patients with DAN have increased rates of sudden cardiac death as well as a higher overall cardiovascular mortality rate. These patients have been found to lack the normal cardiac flow reserve that is activated under conditions of increased demand for myocardial perfusion,¹⁹

which may partially explain the high mortality rate in this population.

In addition to the dysregulation of vascular tone caused by DAN, subjects with diabetes have been found to have decreased bioavailability of NO, a potent vasodilator, as well as increased secretion of the vasoconstrictor endothelin-1. This resulting state of vasoconstriction has been found in subjects with the metabolic syndrome as well as those with diabetes.²⁰ In this situation, the vasculature is in a hyper-constricted state. Not only do hypertension and its concomitant complications result from vasoconstriction, but blood flow is limited to respective tissues. Diabetes decreases NO bioavailability because of either insulin deficiency or defective insulin signaling (insulin resistance) in endothelial cells.²¹ Hyperglycemia also acutely inhibits the production of NO in arterial endothelial cells.²²

In a sense, the ultimate outcome of blood flow to tissues is the transport and exchange of substances between blood and tissue fluid. Thus, despite an appropriate amount of blood flow, any process that inhibits product exchange will impair the homeostasis of the tissue containing the vascular bed. Capillary basement membrane thickening associated with prolonged hyperglycemia is a structural hallmark of diabetic microvascular disease. Thickening of the basement membrane impairs the amount and selectivity of transport of metabolic products and nutrients between the circulation and the tissue.²³ In fact, in skeletal muscle of patients with type 2 diabetes, exercise-stimulated oxygen delivery from the capillaries is delayed, which may account in part for the poor exercise tolerance found in people with type 2 diabetes.²⁴

Transport of substances from the circulation, across the microvessel wall, and into tissue interstitium is regulated by a variety of interdependent mechanisms, including pressure, flow, and size and charge specificity. Paradoxically, basement membrane thickening *increases* microvascular permeability because of alterations in the physical dimensions of the meshwork and changes in the normal electrical charge surrounding the pores between endothelial cells. These abnormalities allow for the transport of large molecules normally excluded from passage across the microvasculature. In clinical terms, transcapillary leak of albumin

in the kidney provides an important indicator of microvascular disease.²⁵ The urine microalbumin test, initially indicated for the detection of early diabetic nephropathy, actually reflects the health of the entire microvasculature. Thus, a patient with a microalbuminuria not only has nephropathy, but also can be assumed to have widespread microvascular disease.²⁶

Inflammation

Inflammation is a normal response to tissue injury or pathogen exposure and is a critical factor in the body's ability to heal itself or to fight off infection. The inflammatory response involves the activation of leukocytes (white blood cells) and is mediated, in part, by a family of cytokines and chemokines. Although inflammation is beneficial, if this response is chronically activated it can have a detrimental effect. Diabetes has long been considered a state of chronic, low-level inflammation,²⁷ and there is some evidence to suggest that this immune activation may precede insulin resistance in diabetic and pre-diabetic states and ultimately may be the factor that initially increases cardiovascular risk in these disease processes.²⁸

Recent evidence suggests cross-talk between the molecular pathways involved in both inflammation and insulin signaling, and this cross-talk may provide clues to the strong relationship between insulin-resistant states (such as the metabolic syndrome and type 2 diabetes), inflammation, and CVD.²⁹ As previously discussed, researchers have found a reduced production of the potent vasodilator NO and an increased secretion of the vasoconstrictor and growth factor endothelin-1 in subjects with the metabolic syndrome, and these abnormalities not only enhance vasoconstriction, but are associated with the release of pro-inflammatory cytokines.³⁰ Proinflammatory cytokines cause or exacerbate injury by a variety of mechanisms including enhanced vascular permeability, programmed cell death (apoptosis), recruitment of invasive leukocytes, and the promotion of reactive oxygen species (ROS) production.³¹

Recently, Pickup and Mattock³² found serum sialic acid, a marker of low-grade inflammation,³³ to be strongly predictive of type 2 diabetes in 128 patients from the United Kingdom who were followed for a mean of 12.8

years. In addition to predicting type 2 diabetes, this marker also predicted cardiovascular mortality independent of other known risk factors for CVD, including pre-existing CVD.³² These observations have led investigators to suspect a common, unknown antecedent³⁴ and to consider chronic inflammation as one candidate for this precursor.

In addition to diabetes, obesity is associated with increased levels of a number of adipokines (cytokines released from adipose tissue), including tumor necrosis factor- α , interleukin 1 β , interleukin 6, and plasminogen activator inhibitor 1 (PAI-1), all linked to the inflammatory response.³⁵ The levels of these pro-inflammatory cytokines typically increase as fat mass increases; however, one exception is the adipokine adiponectin, which has anti-inflammatory properties and is decreased in obese subjects,³⁶ exacerbating the chronic inflammatory nature of obesity. In addition to their endocrine properties, these locally produced cytokines have been found to possess autocrine and paracrine properties that can influence neighboring tissues as well as the entire organism.

Oxidative Stress

As discussed earlier, pro-inflammatory cytokines can enhance the production of ROS. The term ROS refers to a subset of molecules called "free radicals." This term refers to any molecule that contains an unpaired electron in the outer orbital. This unpaired electron makes the molecule highly reactive, seeking to either donate an electron to another compound or take up protons from another compound to obtain a stable electron pair.³⁷ This high reactivity leads to the formation of bonds between the ROS and other compounds, altering the structure and function of the tissue. Because of the reactive propensity of these molecules, ROS can directly damage a number of cell components, such as plasma membranes and organelles.

ROS are produced by the immune system as a way to injure and destroy pathogens, but they are also generated as a result of daily living. Normal metabolism results in the production of ROS, which act as signaling molecules for both physiological and pathophysiological properties. Oxidative stress occurs when the cellular production of ROS exceeds the capacity of anti-oxidant defenses within cells. Numerous

studies have demonstrated chronic oxidative stress in diabetic humans and animals, purportedly related to the metabolism of excess substrates (glucose and fatty acids) present in the hyperglycemic state,³⁸ as well as to the mitochondrial dysfunction associated with insulin resistance.³⁹ For example, plasma levels of hydroperoxides (one ROS) are higher in subjects with type 2 diabetes compared to nondiabetic subjects, and these levels are inversely correlated with the degree of metabolic control.³⁸

The mitochondria are the major source of ROS. At the subcellular level, the etiologies of insulin resistance and diabetes, as well as their complications, are deeply related to defects in mitochondrial function.⁴⁰ The mitochondria produce most of the body's required adenosine triphosphate through the process of oxidative phosphorylation (via the electron transport chain). Oxidative phosphorylation is the major source of ROS under normal physiological conditions.⁴¹ There are two sites in the mitochondrial electron transport chain that generate ROS, and the increased flux of glucose in diabetes has been found to increase ROS production.⁴⁰

Oxidative stress is currently the unifying factor in the development of diabetes complications. In 2004, the Banting Medal for Scientific Achievement, the most prestigious award of the ADA, was given to Michael Brownlee, MD, for his pivotal work in the etiology of diabetes complications. According to Brownlee, there are four mechanisms by which chronic hyperglycemia causes diabetes complications: activation of the polyol pathway; increased formation of advanced glycosylation end products; activation of protein kinase C, an enzyme involved in numerous molecular signaling pathways; and activation of the hexosamine pathway. Through decades of research, Brownlee and his colleagues found that hyperglycemia-induced mitochondrial ROS production activates each of the four major pathways of hyperglycemic damage. Moreover, blocking ROS production or interfering with ROS signaling attenuated the activity of all four pathways.⁴² Thus, oxidative stress is a crucially important concept in the

pathophysiology of the cardiovascular complications in diabetes.

Activated Leukocytes

As previously discussed, the inflammatory response appears to be over-activated in insulin resistance and in diabetes. Leukocytes are major mediators of inflammation. They also contribute to the oxidative stress associated with diabetes. ROS are generated not only from the mitochondria, but also from activated leukocytes. Hokama et al. found that the expression of adhesion proteins on the surface of neutrophils, which suggests activation and ROS production, was significantly increased in diabetes.⁴³ Freedman and Hatchell found that stimulated neutrophils from diabetic animals generated superoxide radical (a type of ROS) at significantly higher rates than did those from normal animals.⁴⁴ Under ischemic conditions, Hokama et al. found that leukocyte accumulation during reperfusion was enhanced in the diabetic coronary microcirculation, suggesting an increased ability of leukocyte-generated ROS to exacerbate tissue damage after experimental myocardial infarction (MI).⁴³ The excess chronic oxidative stress produced in the hyperglycemic state by the mitochondria, as well as the additional acute stress mediated by accumulated leukocytes, may largely explain the mechanism of increased oxidative injury associated with ischemic heart disease in diabetes. This explanation, in turn, aids our understanding of the excessive morbidity and mortality in patients with diabetes after heart attacks when compared to patients without diabetes.

Hypercoagulability

In addition to affecting the leukocytes in the blood, diabetes is also related to a hypercoagulable state. The coagulability of the blood is crucially important in ischemic cardiovascular events because the majority of MI and stroke events are caused by the rupture of atherosclerotic plaque and the resulting occlusion of a major artery by a blood clot (thrombus).

Up to 80% of patients with diabetes die a thrombotic death. Seventy-five percent of these deaths are the result of an MI, and the remainder are the result of cerebrovascular events and complications related to PVD.⁴⁵ The first defense against a thrombotic event is the vascular endothelium. As previ-

ously discussed, diabetes contributes to widespread endothelial dysfunction. The endothelium and the components of the blood are intricately linked, such that clotting signals initiated in the endothelial cell can activate platelets and other blood components, and vice versa.⁴⁶ Patients with diabetes exhibit enhanced activation of platelets and clotting factors in the blood. Increased circulating platelet aggregates, increased platelet aggregation in response to platelet agonists, and the presence of higher plasma levels of platelet coagulation products, such as beta-thromboglobulin, platelet factor 4, and thromboxane B₂, demonstrate platelet hyperactivity in diabetes. Coagulation activation markers, such as prothrombin activation fragment 1+2 and thrombin-anti-thrombin complexes, are also elevated in diabetes. In addition, patients with diabetes have elevated levels of many clotting factors including fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor. Conversely, anticoagulant mechanisms are diminished in diabetes. The fibrinolytic system, the primary means of removing clots, is relatively inhibited in diabetes because of abnormal clot structures that are more resistant to degradation, and also because of an increase in PAI-1.⁴⁷

Clinicians attempt to reverse this hypercoagulable state with aspirin therapy, widely recommended for use as primary prevention against thrombotic events in patients with diabetes. However, numerous studies have suggested that aspirin in recommended doses does not adequately inhibit platelet activity in patients with diabetes. This concept of "aspirin resistance" is controversial and has not been found consistently in all diabetic patient populations, but it may provide insight into the high rates of thrombotic events in diabetes even among those appropriately treated.⁴⁸

In summary, the increase in cardiovascular morbidity and mortality is complex and multifactorial and is usually related to a combination of both macrovascular and microvascular dysfunction. Perhaps no clinical entity demonstrates all of the components of diabetes-related CVD better than the

diabetes patient also diagnosed with chronic heart failure.

Heart Failure

Chronic heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.⁴⁹ Systolic heart failure arises from a compromise in the contractility of the heart and is defined as a left ventricular ejection fraction of < 45%. Diastolic dysfunction interferes with the heart's ability to relax and fill with blood.⁵⁰ Heart failure in a patient with diabetes may arise from myocardial damage resulting from an ischemic, thrombotic event. In this case, endothelial dysfunction, oxidation and glycation of atherogenic lipids, and the hypercoagulability of the blood are major contributors to the patient's resulting heart failure. In many cases, however, heart failure in patients with diabetes may have a non-thrombotic etiology and other pathophysiological factors are at play, as in the case of diabetic cardiomyopathy.

Diabetic cardiomyopathy can be defined as myocardial disease in patients with diabetes that cannot be attributed to any other known CVD, such as hypertension or CAD.⁵¹ Because of the structural and functional changes that occur in diabetic cardiomyopathy, patients with diabetes are vulnerable to heart failure even early in the course of their disease. At least two different epidemiological studies using sensitive diagnostic methods found the prevalence of asymptomatic diastolic dysfunction in patients with type 2 diabetes to be between 52 and 60%, despite meeting clinical criteria for acceptable glycemic control.^{52,53} Left ventricular diastolic dysfunction, characterized by impaired early diastolic filling, prolonged isovolumetric relaxation, and increased atrial filling has even been demonstrated in young patients with type 1 diabetes.⁵⁴

Myocardial damage in the absence of CAD (macrovascular) is most likely related to microvascular dysfunction. Microvascular damage in the diabetic heart may lead to the myocardial injury, fibrosis, and hypertrophy found in diabetic cardiomyopathy.⁵⁵ In type 1 diabetic patients without CAD, impaired coronary flow reserve (dependent on the microvasculature) predicts diastolic dysfunction and may

be related to autonomic neuropathy.⁵⁶ A similar relationship between the magnitude of coronary flow reserve reduction and the degree of myocardial diastolic dysfunction was found in uncomplicated hypertension,⁵⁷ another condition characterized by impaired coronary microcirculation. This association is not surprising because coronary flow occurs predominantly during diastole,⁵⁸ so that normal coronary flow and diastolic dysfunction are interdependent.

In addition to microvascular disease, hyperglycemia is clearly another factor that increases the risk for the development of heart failure in patients with diabetes. In the U.K. Prospective Diabetes Study, every 1% increase in A1C was associated with a 12% increase in heart failure.⁵⁹ In the Strong Heart Study, the presence of type 2 diabetes was associated with left ventricular enlargement and decreased myocardial function in both men and women. In addition, the extent and frequency of diastolic dysfunction was directly proportional to A1C level.⁶⁰ There are a number of mechanisms by which hyperglycemia can contribute to the development and progression of diabetic heart failure. Diastolic dysfunction in diabetic cardiomyopathy is thought to be the result of myocellular hypertrophy and myocardial fibrosis.⁶¹ In the laboratory, there is evidence that cardiac efficiency is decreased in diabetes because of increased fatty acid utilization, which leads to an increased production of ROS.⁶² The increase in oxidative stress in diabetic hearts has been found to decrease NO levels, worsen endothelial function, and induce myocardial injury through stimulation of inflammatory mediators.⁶³

Moreover, a strong correlation was found between left ventricular hypertrophy and markers of chronic inflammation in patients with type 2 diabetes. In the Strong Heart Study, which included 1,299 adults with type 2 diabetes, those with left ventricular hypertrophy had higher levels of fibrinogen and C-reactive protein (both markers of chronic inflammation) and urinary albumin independent of traditional cardiovascular risk factors.⁶⁴ In addition, fibrinogen and C-reactive protein levels were independently and significantly higher in subjects with left ventricular hypertrophy among those without pathological albuminuria, suggesting that the association between

cardiac hypertrophy and low-grade inflammation may precede development of the vascular dysfunction.⁶⁴

In summary, diabetic cardiomyopathy demonstrates multiple mechanisms by which diabetes affects the cardiovascular system. Microvascular disease, including endothelial dysfunction caused by DAN and decreased NO bioavailability is of crucial importance. In addition, the underlying defects of inflammation and oxidative stress contribute to diastolic dysfunction, especially in the presence of poor metabolic control.

CVD accounts for the majority of the morbidity and mortality associated with diabetes. As we continue to learn more about the complex pathophysiology underlying this crucial health problem, more effective therapies for prevention and treatment will emerge.

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