



◀ Piero MARCHETTI, MD, PhD
 Alberto COPPELLI, MD
 Rosa GIANNARELLI, MD, PhD
 Department of Endocrinology
 and Metabolism, Metabolic Unit
 University of Pisa, ITALY

Pathophysiological links between diabetes and heart disease

*by P. Marchetti, A. Coppelli,
 and R. Giannarelli, Italy*

Diabetes mellitus (DM) is a heterogeneous group of metabolic diseases, characterized by hyperglycemia that is caused by defects in insulin secretion, insulin action, or both.¹ There are approximately 200 million diabetic individuals worldwide, with only around half of these being diagnosed, and the number is expected to double by 2030.^{1,2} The vast majority of cases of DM fall into one of two broad categories known as type 1 and type 2. Type 1 DM (T1DM) is characterized by an absolute insulin insufficiency that is caused by the immunological destruction of pancreatic β cells that produce and secrete insulin, and it accounts for 5% to 10% of all cases of DM.³ Type 2 DM (T2DM), which represents approximately 90% of all cases, is more complex in etiology, and is characterized by reduced

Diabetes mellitus is responsible for a spectrum of cardiovascular diseases. Atherosclerotic coronary artery disease is caused by the contribution of several metabolic, hormonal, and hemodynamic factors, which often cluster with obesity and lead to endothelial dysfunction and damage. Independent of the severity of coronary artery lesions, diabetic patients are at an increased risk of developing heart failure; this is the result of what is considered to be a distinct disease process, known as diabetic cardiomyopathy, and which is characterized by structural abnormalities of the myocardium, and systolic as well as diastolic dysfunction. This review focuses on the role of hyperglycemia, dyslipidemia, hypertension, insulin resistance, oxidative stress, enhanced glycosylation, and neural alterations in the creation of the vicious circle that initiates and sustains vascular, myocyte, and interstitial alterations to the diabetic heart.

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Address for correspondence: Professor Piero Marchetti, MD, PhD, Department of Endocrinology and Metabolism, Metabolic Unit, Ospedale Cisanello, Via Paradisa 2, 56100 Pisa, Italy (e-mail: marchant@immr.med.unipi.it)

SELECTED ABBREVIATIONS AND ACRONYMS

AGE	advanced glycation end-product
CAD	coronary artery disease
CAN	cardiac autonomic neuropathy
CAV	cardiac allograft vasculopathy
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DCM	diabetic cardiomyopathy
DM	diabetes mellitus
EDIC	Epidemiology of Diabetes Interventions and Complications
eNOS	endogenous nitric oxide synthase
ERK1/2	extracellular signal-regulated kinase-1/2
FHS	Framingham Heart Study
IDL	intermediate density lipoproteins
IGT	impaired glucose tolerance
IR	insulin receptor
IRS-1	insulin receptor substrate-1
MAP kinase	mitogen-activated protein kinase
MMP	matrix metalloproteinase
MRFIT	Multiple Risk Factor Intervention Trial
NF- κ B	nuclear factor-kappaB
NO	nitric oxide
PI-3K	phosphatidylinositol 3-kinase
RAGE	receptor for advanced glycation end-product
ROS	reactive oxygen species
SUR	sulfonylurea receptor
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study

insulin action (insulin resistance) and a relative insulin deficiency.⁴ The manifestation of frank T2DM occurs along a continuum of insulin resistance, and the progression to full T2DM ensues when pancreatic β -cell hypersecretion of insulin fails to compensate for insulin resistance.⁴

Both T1DM and T2DM increase cardiovascular risk by up to fourfold when compared with the general population, and cardiovascular disease (CVD) accounts for 70% to 75% of deaths in diabetic patients.^{5,6} The association between glucose status and CVD also extends beyond the diabetic threshold, and a relationship between the two can be detected in the presence of impaired glucose tolerance (IGT), impaired fasting glucose, and the upper-normal levels of both the fasting and 2-hour post-oral glucose tolerance tests.⁷ The importance of DM in this regard is also demonstrated by the fact that pancreatic transplantation to cure DM is associated with improved cardiovascular risk profile, better cardiac performance, and reduced progression of vascular lesions.^{8,9}

There is an increased risk of coronary artery disease (CAD) in diabetic patients, which is the result of the contribution of several cardiovascular risk factors; hyperglycemia, insulin resistance, dyslipidemia, hypertension, and endothelial dysfunction. These often cluster with obesity, and they may have a different impact in T1DM and T2DM.^{5,6} Furthermore, independent of CAD, diabetic patients are at an increased risk of developing heart failure through diabetic cardiomyopathy (DCM), which is considered to be a distinct disease process.^{10,11} The concept of this distinct process is based on the assumption that DM leads to changes at the myocardial cellular level, causing structural abnormalities that eventually result in left ventricular hypertrophy, and systolic as well as diastolic dysfunction. Some of the pathophysiological mechanisms linking DM with CAD and DCM will be reviewed in this article. The topic of inflammation is dealt with in a separate article in this issue.

Coronary artery disease

CAD, which causes occlusion of the arteries that supply the heart, is responsible for most of the burden of CVD in patients with DM. The atheromatous plaques found in people with DM are not qualitatively different from those affecting the general population. However, atheroma in DM occurs at an earlier age, is more extensive, more diffuse, involves more distal branches, and is more prone to ulceration and instability.

◆ *The role of hyperglycemia*

Several epidemiological studies have shown that, in diabetic patients, there is no clear glycemic threshold for cardiovascular risk, which increases progressively from values below the diabetic range.^{6,7} In large studies of both T1DM (the Diabetes Control and Complications Trial [DCCT])¹² and T2DM (the United Kingdom Prospective Diabetes Study [UKPDS]),¹³ improved glycemic control was found to have no significant impact on cardiovascular out-

comes. However, an observational follow-up study to DCCT known as the Epidemiology of Diabetes Interventions and Complications (EDIC) study, clearly showed that previous intensive DM treatment was associated with less coronary atherosclerosis—mainly as a result of reduced HbA_{1c} levels.¹⁴ In addition, using the UKPDS data, a prospective observational study lasting over 10 years found that each 1% reduction in HbA_{1c} value was associated with a significant reduction in the DM-related risk of death (21%) and myocardial infarction (14%).¹⁵ As proposed by, among others, the Multiple Risk Factor Intervention Trial (MRFIT),¹⁶ it appears, therefore, that hyperglycemia is a cardiovascular risk factor in its own right that additionally amplifies the effects of other individual risk factors.

Several mechanisms have been suggested to explain how hyperglycemia can contribute to CVD in diabetic patients. High glucose levels lead to the formation of advanced glycation end-products (AGEs), which are proteins or lipids that become glycated after exposure to sugars.¹⁷ The presence and accumulation of AGEs in many different cell types affects extracellular and intracellular structure and function. AGEs cause cross-linkage of vessel wall proteins, leading to thickening and leakage of the vasculature, and the formation of irreversible and abnormal deposits of plasma-derived proteins in the subintimal layers of arteries.^{17,18} In addition, they engage the receptor for AGEs (RAGE), which causes upregulation of nuclear factor-kappaB (NF- κ B), a transcription factor that coordinates the inflammatory response.¹⁸ Furthermore, soluble AGEs activate monocytes and block nitric oxide (NO) activity in the endothelium.^{18,19}

Another important mechanism involves the increased production of free radicals (mainly, but not exclusively, reactive oxygen species [ROS]), caused largely by the overflow of glucose into cells. An ROS is defined as any atom or molecule capable of independent existence, which contains one or more unpaired electrons.²⁰ They include various derivatives of oxygen and nitrogen, such as superoxide, hydroxyl, peroxide, and peroxyxynitrite. These compounds are highly reactive, and can damage protein, RNA, and DNA structures.^{20,21} Normal cellular metabolism does generate ROS, but most of these are quenched by innate antioxidant defense mechanisms to maintain a stable intracellular redox balance. Abnormally high cellular glucose concentrations cause an increase in production of ROS by several mechanisms, as summarized in *Figure 1*. In endothelial cells, the reduced nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) pathway is of particular relevance.²² In addition to the direct endothelial cell damage mediated by ROS, these species can oxidize AGEs (see above) and low-density lipoproteins (LDLs [see below]), thereby increasing the atherogenicity of both.²⁰⁻²²

◆ *The role of insulin resistance*

Insulin resistance is associated with both T1DM and T2DM.¹⁻³ In addition, it may cluster with several classic CVD risk factors, such as visceral obesity, lipid abnormalities, and hypertension, to form a

condition known as the metabolic syndrome.^{23,24} Controversy remains regarding whether insulin resistance per se is involved in the pathogenesis of atherosclerosis.²⁵ At the cellular level, there are two major insulin-regulated pathways, known as the metabolic and mitogenic pathways (Figure 2).²³⁻²⁵ Normally, insulin binds to its receptor (IR) and activates insulin receptor substrate (IRS)-1 by phosphorylation of tyrosine residues. This, in turn, activates phosphatidylinositol 3-kinase (PI-3K), resulting in glucose transport into the cell. In people with obesity, IGT, T2DM, and other insulin-resistant states, there is a severe defect in the activation of IRS-1, and as a result, glucose transport into the cell is impaired. This leads to a rise in blood glucose levels, and the resultant hyperglycemia stimulates insulin release and the development of hyperinsulinemia.

Although the metabolic (IRS-1/PI-3K) pathway is severely impaired in any condition of insulin resistance, the mitogenic pathway (proceeding through mitogen-activated protein [MAP] kinase) seems to retain its sensitivity to insulin, and any prevailing hyperinsulinemia would, therefore, lead to an excessive stimulation of this pathway.²⁴⁻²⁶ This may result in the release of a number of growth and inflammatory factors, and promote proliferation and migration of vascular smooth muscle cells.²²⁻²⁶

◆ The role of plasma lipids

Lipid abnormalities are often found in diabetic patients.²⁷ In T1DM, alterations in lipid metabolism are largely related to the level of glycemic control achieved. Sustained hyperglycemia is associated with increased concentrations of total cholesterol, LDL cholesterol, and triglycerides, and low concentrations of high-density lipoprotein (HDL) cholesterol. All of these abnormalities are reversed with the normalization of blood glucose. The pattern of dyslipidemia in T2DM is determined by the presence of insulin resistance, and is characterized by raised triglyceride concentrations and low HDL cholesterol concentrations. LDL cholesterol levels in T2DM are almost normal, but they are likely to be dominated by the highly atherogenic small, dense LDL particles.²⁸

The mechanisms leading to plasma lipid-induced vascular damage are, in part, understood, and the link between elevated LDL cholesterol and atherosclerosis has long been recognized. In addition to binding with scavenger receptors on monocytes or macrophages to fuel formation of foam cells, LDL particles can undergo oxidation through several mechanisms, thereby contributing importantly to atherogenesis at an early stage.^{20,29} Several study findings are in agreement with this concept: oxidized LDL has been shown to support foam cell formation in vitro; lipids found in human lesions are substantially oxidized; there is evidence for the presence of oxidized LDL in vivo; oxidized LDL has a number of potentially proatherogenic activities; several structurally unrelated antioxidants inhibit atherosclerosis in animals.^{30,31} Small, dense LDL particles have been shown to be more readily oxidized than their larger counterparts in this regard.

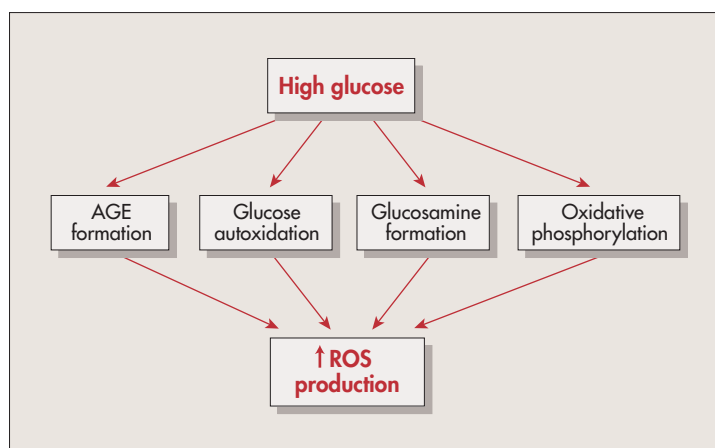


Figure 1. Increased glucose levels cause enhanced production of reactive oxygen species through nonmitochondrial and mitochondrial (oxidative phosphorylation) mechanisms.

Abbreviations: AGE, advanced glycation end-product; ROS, reactive oxygen species.

Furthermore, because of their reduced size, they are likely to penetrate the arterial wall more easily. Finally, it has been demonstrated that these particles have an enhanced affinity for arterial wall proteoglycans, thus prolonging their residence time in the subendothelial space.^{30,31}

Hypertriglyceridemia is considered to be an independent risk factor for CVD in patients with DM.³² It is possible, however, that rather than being actual atherogenic agents themselves, elevated triglycerides serve as a marker of triglyceride-rich remnant lipoprotein increases, and that it is these latter particles that are involved in the development of atherosclerosis. In fact, triglyceride-rich lipoproteins comprise a great variety of nascent and metabolically modified lipoprotein particles that differ in size, density, and lipid and apolipoprotein composition.³³ Studies have shown an inverse relationship between the size of lipoproteins, and their

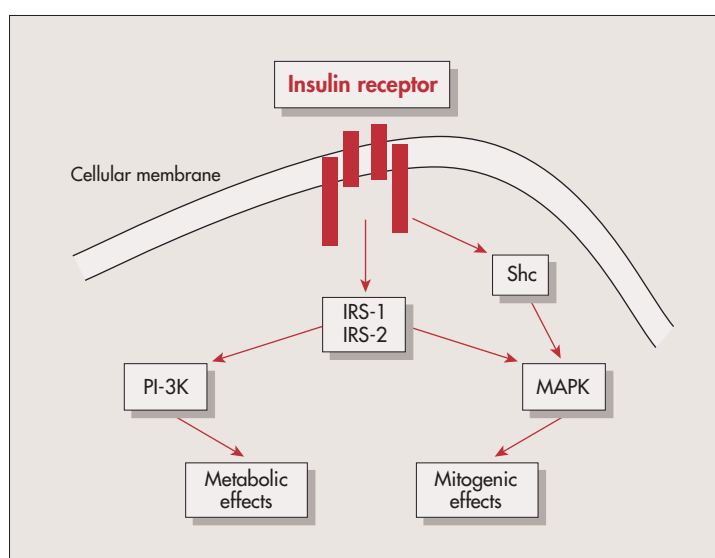


Figure 2. Binding of insulin to its receptor triggers the metabolic and/or mitogenic effects of insulin through IRS-1 and IRS-2 phosphorylation. The metabolic effects are mediated by PI-3 kinase and are blunted in the case of insulin resistance, whereas the mitogenic effects, which are mediated by MAP kinase and Shc, remain sensitive to the action of insulin.

Abbreviations: IRS-1, insulin receptor substrate-1; IRS-2, insulin receptor substrate-2; MAPK, mitogen-activated protein kinase; PI-3K, phosphatidylinositol 3-kinase.

- ◆ Increase reverse cholesterol transport
- ◆ Protect endothelial cells
 - Activate eNOS and NO release
 - Attenuate the expression of VCAM-1, ICAM-1, E-selectin, IL-8
 - Reduce apoptosis by inhibiting caspases and activating protein kinase Akt
- ◆ Reduce oxidative stress
 - Inhibit LDL oxidation by transition metal ions
 - Prevent lipid hydroperoxide formation

Table I. Antiatherogenic roles of HDL particles.
Abbreviations: eNOS, endogenous nitric oxide synthase; HDL, high-density lipoprotein; ICAM-1, induced endothelial cell adhesion molecule-1; IL-8, interleukin 8; LDL, low-density lipoprotein; NO, nitric oxide; VCAM-1, vascular cell adhesion molecule-1.

ability to cross the endothelial barrier to enter the arterial intima. Chylomicrons and large very-low-density lipoproteins (VLDLs) are probably not capable of entering the arterial wall. On the other hand, small VLDLs and intermediate-density lipoproteins (IDLs) can enter the arterial intima.³⁴ As a consequence, certain triglyceride-rich lipoproteins are atherogenic, whereas others are not.

HDL cholesterol, for its part, has protective antiatherogenic actions:^{35,36} HDL particles have a role in reverse cholesterol transport (from nonhepatic cells to the liver), have direct effects on endothelial cells, and possess antioxidant properties (*Table I*).

Compound	Actions
Nitric oxide	↑ Vasodilation, ↓ platelet aggregation
Prostacyclin (PGI ₂ , prostaglandin I ₂)	↑ Vasodilation, ↓ platelet aggregation
Endothelium-derived hyperpolarizing factor	↑ Vasodilation
C-type natriuretic peptide	↑ Vasodilation
Endothelin 1	↑ Vasoconstriction
Angiotensin II	↑ Vasoconstriction
Thromboxane A ₂	↑ Vasoconstriction
Reactive oxygen species	↑ Vasoconstriction
Thrombomodulin	↑ Thrombosis
Tissue plasminogen activator	↓ Fibrinolysis
Plasminogen activator inhibitor-1	↑ Fibrinolysis

Table II. Some of the compounds produced/released by endothelial cells, and their respective main actions.

◆ **The role of hypertension**
 Hypertension affects up to 70% of patients with DM.³⁴ In T1DM, hypertension is usually a manifestation of diabetic nephropathy, while in T2DM it clusters with the other components of the metabolic syndrome—obesity, insulin resistance, and dyslipidemia. Hypertension in DM has some unique characteristics, such as increased salt sensitivity, volume expansion, loss of nocturnal dipping and pulse, and isolated systolic hypertension.^{23,24,37} Several studies have shown that sustained hypertension is associated with structural and functional alterations of both large arteries and arterioles.³⁸ A

key characteristic of the hypertensive artery is increased vascular stiffness, which is probably caused by the accumulation of collagen, as suggested by the observation of increases in collagen type I, III, and IV in hypertensive patients and in animal models of hypertension.³⁸ Remodeling of the arterial walls requires the activity of matrix-degrading enzymes and extracellular matrix protein synthesis. These phenomena are driven, at least in part, by increased NF-κB and MAP kinase activity.³⁹⁻⁴¹ NF-κB regulates the transcription of numerous matrix metalloproteinases (MMPs), including MMP-1, MMP-2, MMP-3, and MMP-9. On the other hand, smooth muscle cell proliferation in hypertension requires extracellular signal-regulated kinase-1/2 (ERK1/2), in a step modulated by MAP kinase.

◆ **The role of endothelial dysfunction**
 Endothelial dysfunction is a precursor to, and an effect of, atherosclerosis. In addition to its obvious role as a mechanical lining, the endothelium also has crucial biological functions, which are mediated by various molecules produced and released by the endothelial cells, and include regulation of leukocyte adhesion and trafficking, prevention of platelet adhesion, and regulation of blood flow via modulation of vessel patency (*Table II*).⁴²

In DM, hyperglycemia promotes the formation of ROS and AGEs, which, in addition to the proatherosclerotic actions mentioned above, stimulate the endothelial expression of proinflammatory cytokines such as interleukin-6 and monocyte chemoattractant protein-1, as well as leukocyte adhesion molecules.⁴³ In addition, increased oxidative stress leads to quenching of NO and degradation of endogenous nitric oxide synthase (eNOS) cofactor tetrahydrobiopterin (BH4).⁴²⁻⁴⁴ The presence of insulin resistance also causes alterations to the PI-3K/Akt pathway (see above), which, in turn, lead to a marked decrease in eNOS activation. Taken together, these alterations confer a strong proatherogenic profile, which plays a major role in the development of CAD.

Interestingly, a role has been proposed for C-peptide in the modulation of endothelial function.⁴⁵ C-peptide is cosecreted with insulin (both are derived from the common precursor proinsulin), and patients with T1DM lack C-peptide as well as insulin. C-peptide was previously considered to be biologically inert; however, it has recently been reported that the molecule can have a biological function,^{45,46} and enhances skeletal muscle, skin, and renal blood flow.^{45,47} It was recently demonstrated that, in T1DM patients, impaired myocardial perfusion can be improved by replenishing C-peptide levels. C-peptide induces vasodilation mainly via the endothelium-dependent mechanism. It increases NO concentrations in a dose-dependent manner, and eNOS inhibition has been reported to abolish C-peptide-induced vasodilation and NO release.^{45,48}

Diabetic cardiomyopathy

DCM is a disease of the myocardium, associated with DM, which leads to cardiac dysfunction.^{10,11} As previously discussed, CAD is the most common form

of cardiac manifestation in DM. However, nonischemic heart failure is also an important cause of morbidity and mortality in diabetic patients. In the Framingham Heart Study (FHS), the relative risk of congestive heart failure was up to fivefold higher in people with diabetes than in the general population.⁴⁹ Early pathological features of DCM include nonspecific interstitial changes within preserved monocytes, which progress to more marked interstitial and perivascular fibrosis, with deposition of periodic acid Schiff (PAS)-positive material, myocyte hypertrophy, microvascular alterations (thickening of the basement membrane and microaneurysms), ventricular dilatation, and diastolic dysfunction with either decreased or maintained systolic function.^{10,11} Metabolic and hormonal factors, autonomic neuropathy, and microangiopathic alterations are the main etiopathologic factors. Some of these factors (in particular AGEs, oxidative stress, and endothelial alterations) have been discussed above; below we will focus on a few additional points.

◆ *The role of metabolic and hormonal factors*

The overall myocardial response to the diabetic milieu is a reduction in glucose uptake and oxidation, and an increase in fatty acid uptake and oxidation.⁵⁰ It has been proposed that in people with DM, myocytes cannot metabolize pyruvate in the normal manner, and in the presence of an energy deficit (such as that caused by ischemia), they sustain reperfusion injuries.^{10,11,50} Furthermore, accumulation of pyruvate inhibits glycolysis, therefore more glucose is directed to form glycogen. As adenosine triphosphate (ATP) derived from glycolysis is preferentially used by the myocyte for calcium reuptake into the sarcoplasmic reticulum, reduced glycolysis results in impaired myocyte relaxation. In the earlier stages of DM, glucose metabolism is regulated by compensatory hyperglycemia, and at the same time, the myocyte responds to the increased fatty acid levels resulting from insulin resistance and increased systemic lipolysis by upregulating mitochondrial β -oxidation. Exacerbation of chronic hyperglycemia induces lipid esterification and intracellular triglyceride accumulation, which lead to ceramide (a toxic lipid compound) production, oxidative stress, apoptosis, and decreased myocardial function.⁵¹ In addition, as discussed above, hyperglycemia increases the oxidative stress and glycosylation processes. Among the consequences of this are that glycosylation of the p53 protein leads to activation of angiotensin II synthesis, which in turn, contributes to enhanced apoptosis and necrosis.⁵² Furthermore, angiotensin II has dose-dependent effects on collagen production and secretion, thus favoring interstitial fibrosis.⁵² Hyperglycemia can also activate the protein kinase C β_{II} pathway, again promoting myocardial necrosis and fibrosis.⁵³

◆ *The role of cardiac autonomic neuropathy*

Cardiac autonomic neuropathy (CAN) has been associated with myocardial dysfunction, and the development of CAN results in a 44% to 85% survival reduction in patients with DM.⁵⁴ Other studies found

that, in coronary resistance vessels, CAN was associated with an impaired vasodilator response to increased sympathetic stimulation, and that about 20% of patients with DM who did not have ischemic heart disease had abnormal diastolic filling that was related to the severity of CAN.^{54,55} Similarly, ventricular filling abnormalities are most prominent in patients with CAN, and a correlation has been found between myocardial sympathetic innervation as recorded on scintigraphy, and the E/A ratio (ratio of early to late peak mitral filling wave velocities in Doppler echocardiography), providing evidence that an abnormal sympathetic innervation of the heart might contribute to a disturbance in left ventricular filling.⁵⁶

Catecholamines regulate the contractility of cardiac myocytes by acting on sarcoplasmic reticulum calcium uptake, and under conditions of β -adrenergic receptor stimulation, cardiac performance is enhanced.⁵⁷ These effects are mediated by cAMP-dependent phosphorylation of proteins located in the sarcolemma, the membrane of the sarcoplasmic reticulum, and in the myofibrils of the cardiomyocytes. In DM, the cardiac β -adrenergic system may be enhanced, which can induce myocyte hypertrophy, interstitial fibrosis, and reduced contractile function, accompanied by myocyte apoptosis.^{10,11} On the other hand, α -adrenergic stimulation, which has antiapoptotic effects, seems to be decreased in DM.⁵⁸

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) is a type of cardiovascular disease that occurs in heart transplant recipients.^{59,60} It is a rapidly progressive form of atherosclerosis characterized in its early stages by intimal proliferation, and in its later stages by luminal stenosis of epicardial branches, occlusion of smaller arteries, and myocardial infarction. There are some important differences between CAV and classic coronary atherosclerosis.^{59,60} In CAV, intimal proliferation is concentric rather than eccentric, and the lesions are diffuse, involving both distal and proximal portions of the coronary tree. Calcification is uncommon, and the elastic lamina remains intact. Both immunologic and nonimmunologic mechanisms are involved in the pathogenesis of CAV. The initiating event is subclinical endothelial cell injury in the coronary graft, probably caused by ischemia–reperfusion damage or the host-versus-graft immune response. This leads to a cascade of immunologic processes involving cytokines, inflammatory mediators, complement activation, and leukocyte adhesion molecules.⁶¹ These changes produce inflammation, and ultimately, thrombosis, smooth muscle cell proliferation, and vessel constriction. Among the nonimmunologic factors, DM—both preexisting and new-onset after transplantation (mainly caused by immunosuppression)^{59,62}—and the metabolic abnormalities associated with insulin resistance,⁵⁹ play a major role in accelerating vascular damage, probably through the same mechanisms described above for CAD in the nontransplant setting.

A role for oral insulin secretagogue agents?

Insulin secretagogues (sulfonylureas and glinides) are widely used in T2DM therapy. They bind to sulfonylurea receptors on the β -cell membrane,^{63,64} causing closure of the ATP-sensitive potassium channel (K_{ATP} channel) and depolarization of the cell membrane. This, in turn, opens voltage-gated calcium channels, leading to an influx of calcium ions and subsequent secretion of preformed insulin granules. The K_{ATP} channels are formed of two subunits: a sulfonylurea receptor (SUR), which binds sulfonylurea agents, and the actual potassium pore.⁶⁴ K_{ATP} channels are found in several cell types that share a common Kir6.2 unit, but have different sulfonylurea receptors. In particular, the isoform SUR1 is located in the pancreatic β cell, and SUR2A is in cardiac cells.^{65,66}

Structurally, sulfonylurea agents can have both the sulfonylurea component and a benzamido group, whereas glinides are derived from the benzamido nonsulfonylurea portion. It has been proposed that SUR1 has both sulfonylurea and benzamido binding sites, whereas SUR2A has only a benzamido binding site.^{65,66} As a consequence, agents that have both portions (such as glibenclamide) interact with both the pancreatic β cell and the cardiac cell, and those having only the sulfonylurea portion (such as gliclazide) bind with the β cell only. The clinical significance of these characteristics is

still a matter for debate. However, it has been observed that inhibition of K_{ATP} in the heart is associated with impaired ischemic preconditioning and reduced coronary vasodilation in response to myocardial ischemia.^{67,68}

Conclusions

Diabetic heart disease is caused by complex interactions that result from overlapping mechanisms. The driving forces are related to the phenotypic alterations associated with diabetes—in particular hyperglycemia, dyslipidemia, hypertension, and possibly insulin resistance. A vicious circle develops, leading to increased oxidative stress and enhanced glycosylation of several humoral and vessel wall proteins, which cause endothelial damage and structural changes in coronary arteries. In turn, damaged endothelial cells can become a source of ROS and reactive nitrogen species in addition to other factors, sustaining the proatherosclerotic process. Some of these pathways are also involved in the development of DCM, a condition in which, among other factors, myocyte substrate utilization and neural influences play a major role. At least a few of these mechanisms are involved in coronary artery damage observed in specific situations such as cardiac allograft coronaropathy. Further studies are needed to elucidate the possible beneficial role of oral antidiabetic agents in relation to diabetic heart disease. □

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RELATIONS PHYSIOPATHOLOGIQUES ENTRE DIABÈTE ET MALADIE CARDIAQUE

Le diabète est à l'origine de nombreuses maladies cardiovasculaires. Plusieurs facteurs métaboliques, hormonaux et hémodynamiques, souvent combinés à l'obésité, et conduisant à des lésions et à une dysfonction endothéliale, contribuent à la coronaropathie athéroscléreuse. Les diabétiques ont plus de risques de développer une insuffisance cardiaque, indépendamment de la sévérité des lésions coronaires. Celle-ci résulte d'un processus pathologique reconnu comme étant distinct, dénommé cardiomyopathie diabétique, qui se caractérise par des anomalies structurelles du myocarde ainsi que par une dysfonction systolique ou diastolique. Cet article évoque le rôle de l'hyperglycémie, de la dyslipidémie, de l'hypertension, de la résistance à l'insuline, du stress oxydatif, de l'exacerbation de la glycosylation et des altérations nerveuses dans la création du cercle vicieux qui instaure et maintient les altérations vasculaires, myocytaires et interstitielles au niveau du cœur diabétique.