Diabetes and Cardiovascular Disease: Explaining the Relationship

Zubin Punthakee, MD, MSc,*† Geoff H. Werstuck, PhD,‡
Hertzel C. Gerstein, MD, MSc*†

*Division of Endocrinology and Metabolism, †Population Health Research Institute, and
‡Division of Hematology and Thromboembolism, Department of Medicine,
McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

Diabetes is a risk factor for cardiovascular disease. However, even elevated glucose levels below the diabetic range increase cardiovascular risk. There are several possible explanations for this relationship. First, glucose and its metabolites have direct toxic effects on vascular endothelium. Second, abnormal glucose is evidence of absolute or relative insulin deficiency, which can predispose patients to cardiovascular disease via endothelial dysfunction, lipid abnormalities, and inflammation. Third, antecedent factors, such as toxins, abnormal energy storage, and hypertension, may contribute to the development of both diabetes and cardiovascular disease. Whether glucose lowering can reduce the risk of cardiovascular disease is currently being studied in a number of large trials.

[Rev Cardiovasc Med. *2007;8(3):145-153*]

Key words: Diabetes mellitus • Dysglycemia • Cardiovascular disease • Insulin • Glucose lowering

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia that is associated with a high future risk of cardiovascular disease (CVD) and other serious health-related consequences. The incidence of CVD in men and women with DM is up to 3 to 4 times higher than in unaffected individuals.[1-3] Furthermore, DM is associated with a CVD mortality rate that exceeds 70%, and people with DM are 2 to 3 times more likely to die from CVD causes than people with no history of DM, even after controlling for other CVD risk factors.[4] They are also at high risk of diseases associated with

Table 1
Cardiovascular Event Rates for Various Outcomes by Baseline Cardiovascular Inclusion Criteria in People With Diabetes

	Outcome			
Inclusion Criteria	**MI, Angina, Stroke/TIA, CHF, Revascularization**	**MI, Stroke, Revascularization/ Amputation**	**CVD Death, MI, Stroke**	**CVD Death, MI**
Prior CVD*	N/A	N/A	3.7%[88] 4.1%[81]	7.2%[91] 4.3%[92] 4.2%[93]
Prior CVD* or ≥ 1 CVD risk factor†	3.6%[83‡] 4.0%[84]	5.2%[86]	N/A	2.6%[86] 1.5%[84]
≥ 1 CVD risk factor†	N/A	6.1%[87]	4.0%[89‡]	2.3%[65]
No prior CVD* and ≥ 1 CVD risk factor†	2.4%[85]	N/A	N/A	N/A
No CVD-related inclusion criteria	N/A	N/A	1.3%[78] 1.0%[90] 2.1%[80]	1.1%[89]

*CVD event or evidence of atherosclerosis/ischemia.
†Hypertension, left ventricular hypertrophy, retinopathy, albuminuria, smoking, dyslipidemia.
‡Required 2 or 3 risk factors.
MI, myocardial infarction; TIA, transient ischemic attack; CHF, congestive heart failure; CVD, cardiovascular disease; N/A, not available.

CVD and atherosclerosis, including hypertension, renal failure, limb amputation, cognitive decline, premature death, retinal disease leading to blindness, and erectile dysfunction. In 2002, DM and its consequences cost Americans close to $130 billion in direct and indirect health care costs, of which at least 20% to 25% was related to CVD.[5]

The actual incidence of CVD in people with diabetes varies depending on the population studied and the definition of CVD used. Table 1 summarizes the incidence of CVD events in the control groups of clinical trials that reported CVD incidence in people with diabetes. The studies are grouped according to CVD-related inclusion criteria and CVD outcomes. The annualized incidence of the composite of CVD death, myocardial infarction (MI), or stroke was 3.7% to 4.1% in people with previous CVD or at least 2 CVD risk factors, as compared with 1% to 2.1% in people without CVD or risk factors.

This article will examine dysglycemia and CVD, including the direct effect of elevated glucose levels and the possibility that both dysglycemia and CVD could be related to some antecedent and independent determinant. It will also review approaches to preventing CVD in diabetes.

Dysglycemia and CVD

Epidemiologic evidence indicates that the diagnosis of diabetes may not be as relevant to cardiovascular risk as the degree of abnormal glucose homeostasis. The diagnostic criteria for diabetes—a confirmed fasting plasma glucose (FPG) at least 126 mg/dL (7.0 mmol/L) or plasma glucose at least 200 mg/dL (11.1 mmol/L) 2 hours after an oral glucose load (2-hour glucose)—were chosen because they identified individuals at high risk of retinopathy.[6] However, typical measurements of glycemia, including FPG, 2-hour plasma glucose, and glycated hemoglobin (A_{1c}, which correlates with mean glucose levels over the previous 2 to 3 months[7]), are all associated with CVD, in a progressive relationship that extends to individuals with glucose abnormalities that are close to the normal range. For example, in a meta-regression analysis of more than 20 prospective studies comprising 1.2 million person-years of follow-up, the risk of incident CVD rose progressively as FPG and post-load glucose levels rose above 75 mg/dL (4.2 mmol/L).[8] In 2 recent meta-regression analyses of studies including diabetic and nondiabetic participants, a 1 mmol/L rise in FPG was associated with an 18% (95% confidence interval [CI], 11-25) rise in the risk of CVD[9] and a 23% (95% CI, 19-27) increase in ischemic heart disease.[10]

Epidemiologic evidence indicates that the diagnosis of diabetes may not be as relevant to cardiovascular risk as the degree of abnormal glucose homeostasis.

The progressive relationship between glycemia and CVD is also apparent when hemoglobin A_{1c} is used as a marker of glycemia.[11] A recent meta-analysis reported that in

people with or without diabetes, a 1% rise in hemoglobin A_{1c} is associated with a 17% rise in the risk of CVD (95% CI, 1-37).[9] This observation was supported by a large European cohort study in which a 1% rise in hemoglobin A_{1c} was associated with a 20% to 25% increase in CVD events.[12] People with diabetes were included in this study; however, hemoglobin A_{1c} remained an independent predictor of CVD events after controlling for a history of diabetes as well as for age and other risk factors. These findings further highlight the importance of glycemia, rather than the presence or absence of diabetes per se, as a CVD risk factor.

These data are also supported by other observations. People with double- or triple-artery coronary disease have a greater than 60% prevalence of impaired glucose tolerance.[13] At least 2 out of 3 patients who present with an MI have persistent evidence of either diabetes, impaired glucose tolerance, or a fasting glucose level of at least 110 mg/dL (6.1 mmol/L).[14,15] In addition, there is a direct relationship between the glucose level measured at the time of an MI, acute coronary insufficiency, or stroke[16-20] and the subsequent risk of death or disability (regardless of antecedent diabetes status).

The Relationship Between Dysglycemia and CVD

Three related explanations may account for the link between elevated glucose levels and CVD (Figure 1): a direct effect of elevated glucose levels; a decreased insulin effect due to reduced insulin secretion, reduced insulin action (ie, insulin resistance), or a combination of these abnormalities; and an underlying genetic and/or environmental abnormality that predisposes individuals to both diabetes and CVD.[21,22]

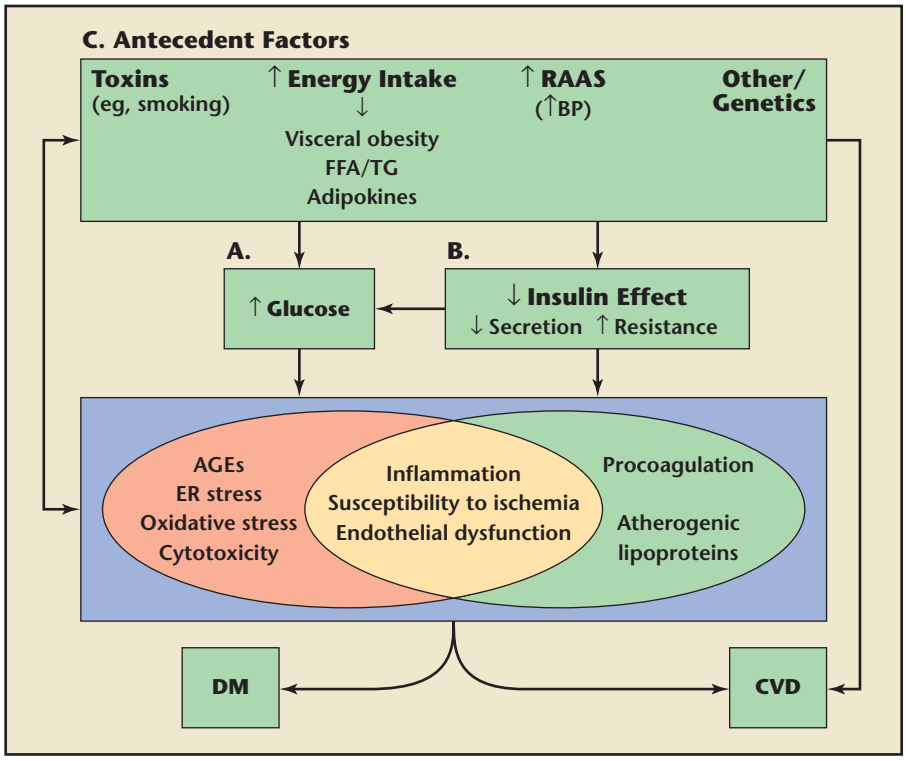
Direct Effect of Elevated Glucose Levels

Glucose is a key substrate for energy production in all cells. Upon entry into the cell, glucose is immediately phosphorylated by hexokinase to glucose 6-phosphate, much of which is shunted through the glycolytic pathway, where it generates adenosine triphosphate and metabolites. Exposure of cells to higher levels of glucose than are needed to satisfy normal energy requirements leads to increased concentrations of metabolites and activation of at least 4 metabolic pathways that have been linked to endothelial cell dysfunction and atherosclerosis.[23]

First, excess glucose increases flux through the polyol pathway and is converted to sorbitol, which is subsequently oxidized to fructose. This process depletes intracellular levels of the antioxidant, reduces glutathione, and increases susceptibility to oxidative stress.[23]

Second, excess fructose-6-phosphate is converted to glucosamine 6-phosphate and UDP-*N*-acetylglucosamine by the hexosamine pathway. This conversion promotes O-linked glycosylation of transcription factors,[24] nuclear pore proteins,[25] and signaling factors,[26] thereby altering their function, stability, and/or activity. It also promotes transcription of proinflammatory and prothrombotic factors, including transforming growth factor alpha (TGF-α), transforming growth factor

Figure 1. *Possible pathophysiologic links between diabetes and CVD. Elevated glucose* **(A)** *and insufficient insulin effect* **(B)** *promote a variety of processes that are associated with both diabetes and CVD; some or all of these processes may also cause these 2 conditions. Antecedent or proximal factors* **(C)** *may act through glucose elevation* **(A)**, *reduced insulin effect* **(B)**, *or other mechanisms to promote both diabetes and CVD. FFA, free fatty acids; TG, triglycerides; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system; AGEs, advanced glycation end products; ER, endoplasmic reticulum; DM, diabetes; CVD, cardiovascular disease.* www.medreviews.com



beta (TGF-β), and plasminogen activator inhibitor 1 (PAI-1).[27,28] Of particular interest is the observation that activation of the hexosamine pathway also leads to glucosamine-induced endoplasmic reticulum stress in cells that are relevant to atherogenesis, including human macrophages, vascular smooth muscle cells, and endothelial cells.[29,30] Endoplasmic reticulum stress-inducing agents activate NF-κ B, the transcription factor responsible for promoting inflammatory gene expression.[31] In addition, endoplasmic reticulum stress activates caspases and promotes apoptosis of human aortic endothelial cells and hepatocytes.[30,32]

Third, excess glyceraldehyde-3-phosphate increases dihydroxyacetone phosphate and production of diacylglycerol and, subsequently, protein kinase C. This molecule activates a variety of processes that reduce nitric oxide synthase and fibrinolysis and increase endothelin, vascular permeability, inflammatory gene expression, and the generation of reactive oxygen species.[23]

Fourth, the increase in glyceraldehyde-3-phosphate also promotes increased production of methylglyoxal and subsequent intracellular and extracellular formation of advanced glycation end products. These in turn can impair the activity of intracellular, membrane, and plasma proteins (eg, transcription factors, collagen, and lipoproteins), promote macrophage/scavenger cell activity, and activate inflammatory pathways and production of reactive oxygen species.[23]

It has recently been suggested that these 4 cytoplasmic processes are amplified by a fifth mitochondrial process. Increased glycolysis, as well as excess β-cell oxidation of fatty acids delivered as a consequence of a reduced insulin effect (that initially led to the high glucose levels), directly increases the flux of electrons through the mitochondrial electron transport chain. This increases the generation of reactive oxygen species that are directly cytotoxic and that reduce the activity of the glycolytic intracellular enzyme glyceraldehyde phosphate dehydrogenase. This process leads to further accumulation of intracellular metabolites of glycolysis, further activation of the pathways discussed, and further production of toxic intermediates.[23]

The toxic effects of chronic hyperglycemia on the vasculature may lead to permanent changes in cellular function as a result of damage to mitochondrial or nuclear DNA,[23,33] even after hyperglycemia is corrected.

Reduced Insulin Effect

Insulin is the key hormone involved in glucose homeostasis and is essential for the maintenance of normoglycemia. Any deficiency in the amount or activity of insulin at its key metabolic targets (muscle, fat, liver, and glucagon-secreting α cells) leads to some degree of glucose elevation and the metabolic consequences discussed above. This glucose elevation is a powerful stimulus for insulin secretion and hyperinsulinemia, although these processes may be insufficient to restore glucose levels to normal. Careful measurement in apparently "normoglycemic" individuals with substantial insulin resistance has demonstrated slight elevations in glucose levels.[34] Thus, what is detected as insulin resistance may in fact be subtle degrees of β cell dysfunction leading to high insulin levels that are nevertheless insufficiently high to maintain a normal glucometabolic state.

This observation has several implications. First, a reduced physiologic effect of insulin due to either absolute insulin deficiency and/or relative insulin deficiency (ie, insulin resistance) causes glucose elevation and the consequences noted above. Second, insulin is a powerful inhibitor of lipolysis and the lipolytic effect of stress hormones (especially cortisol and catecholamines). The increased free fatty acid (FFA) flux resulting from a reduced physiologic effect of insulin can promote further insulin resistance[35]; lead to ectopic fat deposition in islet cells[36] and subsequent β-cell damage (thereby magnifying insulin deficiency); stimulate the synthesis of atherogenic lipoproteins[35]; and inhibit glycolytic metabolism and anaerobic energy production in ischemic cardiac muscle, thereby increasing the damage done by an ischemic insult.[37-39] Third, insulin reduces inflammation—by reducing TNF-α, the intracellular adhesion molecule 1, monocyte and macrophage cytokines,[40,41] and superoxide anion—which suggests that insulin deficiency may be proinflammatory. These mediators are thought to directly contribute to the development of the necrotic core of the atherosclerotic lesion. Fourth, insulin reduces PAI-1 levels; an insufficient physiologic effect of insulin therefore represents a procoagulant stimulus. Fifth, insulin deficiency may reduce ischemic preconditioning, making cardiac muscle more susceptible to ischemic damage.[40,42] Finally, lack of insulin reduces endothelial nitric oxide synthesis and vasodilation, especially in response to ischemia,[40,42] and insulin may also improve endothelial function.[43]

A Predisposition to Both Dysglycemia and CVD

The possibility that both dysglycemia and CVD could be related to some antecedent and independent determinant is very difficult to study. Environmental toxins, excess

energy intake, and hypertension are all potential candidates.

Environmental Toxins

There is limited evidence to suggest that exposure to certain environmental toxins predisposes the development of both diabetes and atherosclerosis. Several cross-sectional and ecologic studies indicate that subjects who were exposed to high levels of arsenic in drinking water or in occupational settings had a risk of developing type 2 diabetes that was up to 6 times higher than that in unexposed controls. There was evidence of a dose-response relationship. The effect of arsenic may be mediated by impaired insulin signaling.[44] Other studies indicate that chronic arsenic exposure is associated with ischemic heart disease and carotid atherosclerosis and may lead to increased platelet aggregation.[45]

Cadmium is another environmental pollutant that accumulates in the pancreas and is associated with type 2 diabetes in a dose-dependent manner.[46] Cadmium has been associated with endothelial toxicity, hypertension, and atherosclerosis.[47] Furthermore, cigarette smoking, which is a strong risk factor for heart disease, is associated with a 20% to 34% increased risk of developing type 2 diabetes.[48]

As research into environmental toxins and endocrine disruptors expands, additional associations are likely to be discovered. The challenge in this field is to design high-quality observational studies.

Excess Energy Intake/Abnormal Storage of Excess Energy

A more ubiquitous environmental agent is food. Over the past half century, there has been an increased availability of energy-dense, processed foods, and a proliferation of technology that promotes sedentary behavior. There has been a concomitant increase in the prevalence of obesity—increased and ectopic storage of consumed energy as fat. As energy surplus increases, storage shifts increasingly from subcutaneous to visceral fat, which has a more rapid turnover of triglycerides and a more deleterious metabolic and atherogenic secretory profile.[49] Recently, attention has also focused on epicardial fat, which has similar embryonic origins and metabolic characteristics as abdominal visceral fat, and which is in close proximity to the coronary arteries and cardiac muscle. This visceral fat depot has also been associated with coronary atherosclerosis measured angiographically.[50]

Several mechanisms may account for the link between visceral fat and both metabolic and cardiovascular abnormalities. First, FFAs are easily released from visceral fat stores by lipolysis, which is resistant to suppression by insulin.[51] These FFAs drain directly into the portal circulation and, from there, into the liver and pancreas. As described above, ectopic deposition in the liver leads to hepatic steatosis, hepatic gluconeogenesis, and a rise in hepatic glucose output.[52] Ectopic fat deposition in the pancreas leads to reduction in insulin secretion.[53] Furthermore, ectopic fat deposition in muscle reduces insulin sensitivity and glucose uptake peripherally. All of these consequences are features of diabetes. The cardiovascular effects of excess energy flux include overproduction of very low-density lipoprotein and apolipoprotein B due to increased FFA uptake by the liver, which results in elevated triglycerides that are also associated with low high-density lipoprotein (HDL) cholesterol and atherogenic small, dense low-density lipoprotein (LDL). Furthermore, excess FFAs increase the oxygen demands of ischemic myocardium and reduce the use of glucose as a metabolic fuel by the heart.

Unregulated FFA release has indirect effects as well. Visceral fat is a source of other hormones and cytokines, collectively called *adipokines*, which have various effects on fat, muscle, the liver, the pancreas, the endothelium, and reticuloendothelial tissues. Adipokines likely have a role in metabolism and inflammation. For example, macrophages in expanding visceral fat produce metabolically harmful inflammatory adipokines, such as TNF-α and interleukin-6, which have themselves been associated with diabetes and insulin resistance in type 2 diabetes.[54-56] Conversely, visceral adipose tissue secretion of adiponectin, an insulin-sensitizing adipokine, decreases in obesity.[57] Low adiponectin is a predictor of incident type 2 diabetes[55,58,59] and coronary artery disease.[60]

Hypertension

Another risk factor common to both diabetes and CVD is hypertension. High blood pressure is present in 66% to 74% of people with diabetes.[61-63] Furthermore, epidemiologic evidence suggests that hypertension is a risk factor for the development of diabetes. One prospective study found that people with hypertension had a 2.4-fold higher incidence of diabetes than people without hypertension.[64] In addition, an epidemiologic analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found a 1% increased risk of incident diabetes for every mm Hg rise in systolic blood pressure after adjusting for the antihypertensive regimen.[65]

It is well known that hypertension is a cardiovascular risk factor. One meta-analysis of observational studies

including over 12.7 million person-years of follow-up estimated a doubling of mortality from vascular causes for every 20 mm Hg increase in systolic blood pressure or 10 mm Hg increase in diastolic blood pressure for people ages 40 to 69.[66]

One explanation for the increased risk of diabetes in hypertension is activation of the renin-angiotensin system. Both angiotensin II–mediated pancreatic vasoconstriction[67] and aldosterone-mediated hypokalemia[68] inhibit glucose-induced insulin release from the β cell. In addition, blockade of the renin-angiotensin system with angiotensin-converting enzyme (ACE) inhibitors reduces the counterregulatory hormone norepinephrine[69] and improves peripheral insulin sensitivity.[70] Furthermore, a large body of evidence suggests that blocking the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers prevents the development of diabetes in people with hypertension, heart disease, or heart failure,[71] and reduces glucose levels (both fasting and after an oral glucose load in people with impaired glucose tolerance or impaired fasting glucose).[72]

Some of the mechanisms by which high blood pressure may contribute to vascular disease include increased sympathetic drive, endothelial dysfunction, generation of oxygen free radicals, inflammation of the vessel wall, and left ventricular hypertrophy—all of which are at least partially mediated by the renin-angiotensin system.[73] In addition to the cardiovascular benefit seen with all blood pressure–lowering drugs,[74] ACE inhibition may have further benefit among high-risk individuals.[75] Particularly in patients with diabetes, ACE inhibitors or angiotensin receptor blockers are often the first-line antihypertensive agents.

Preventing CVD in Diabetes

The increased risk of CVD in people with diabetes has led to aggressive interventions to modify CVD risk factors, including lowering of LDL cholesterol. Smoking cessation is another widely accepted intervention. Blood pressure lowering has a significant body of evidence supporting its cardiovascular benefit[74] in this population.

Conversely, interventions to reduce abnormal energy storage and its effects are not strongly supported at this time. To date, clinical trials of weight loss strategies in diabetes, including lifestyle modification or the drugs sibutramine, orlistat, and rimonabant, have not evaluated cardiovascular outcomes. They have, however, found improvements in cardiovascular risk factors, including blood pressure, triglycerides, HDL cholesterol, and LDL cholesterol.[76] Studies of triglyceride lowering with fenofibrate provided weak evidence for cardiovascular benefit in patients with diabetes.[77,78]

Whether glucose lowering (by increasing the insulin effect) has cardiovascular benefit is an actively researched question with some positive supporting data. The Diabetes Control and Complications Trial in 1441 people with type 1 diabetes found that a 6-year period of intensive glycemic control (A_{1c} 7.2% vs 9.0%) led to a 42% reduction in CVD outcomes after 11 more years of passive follow-up. During passive follow-up, glycemic control was not different between the groups.[79] The United Kingdom Prospective Diabetes Study (UKPDS) showed a trend toward reduced risk of MI over 10 years (relative risk reduction, 16%; 95% CI, 0-29; $P = .052$) in 3867 people with type 2 diabetes using an intensive intervention that achieved a median A_{1c} of 7.0% compared with 7.9% in the conventional treatment group.[80] In the recent Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study of 5238 patients with type 2 diabetes, subjects using pioglitazone showed a trend toward reduction in the primary composite CVD outcome (relative risk reduction, 10%; $P = .095$), with a 0.6% reduction in A_{1c}.[81]

Several ongoing clinical trials designed to specifically test the hypothesis of cardiovascular risk reduction by glucose lowering are expected to report results by 2010.[82] The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial will evaluate a target FPG of 5.3 mmol/L or less using glargine insulin versus usual care in people with impaired fasting glucose, impaired glucose tolerance, or early diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study will evaluate the effects of a target A_{1c} of less than 6.0% versus 7.5%, using all available therapies in subjects with type 2 diabetes. The Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation (ADVANCE) trial will evaluate a sulfonylurea-based target of less than 6.5% versus conventional treatment in people with type 2 diabetes. The Veteran Affairs Diabetes Trial (VADT) will evaluate a target A_{1c} of less than 6.0% versus 8% to 9%, using sequential addition and titration of various oral agents and insulins.

Conclusion

There is a progressive relationship between glycemia and cardiovascular risk. The pathophysiologic explanations are difficult to discern, but involve high glucose levels, broader effects of deficient insulin action, and other environmental and/or genetic factors that predispose patients to both dysglycemia and CVD. Ongoing trials are testing the possibility

that CVD can be reduced by therapeutic strategies targeting these abnormalities. ■

Acknowledgments: Dr. Punthakee holds a McMaster University Department of Medicine Internal Career Research Award. Dr. Werstuck holds a New Investigator Award from the Heart and Stroke Foundation of Canada. Dr. Gerstein holds the McMaster University Population Health Institute Chair in Diabetes Research (sponsored by Aventis). Editorial support for this article was provided by sanofi-aventis US.

References

1. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care*. 2000;23:962-968.
2. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care*. 1979;2:120-126.
3. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;368:29-36.
4. Gerstein HC, Malmberg K, Capes S, Yusuf S. Cardiovascular diseases. In: Gerstein HC, Haynes RB, eds. *Evidence-Based Diabetes Care*. Hamilton, Ontario: BC Decker Inc; 2001: 488-514.
5. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917-932.
6. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183-1197.
7. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care*. 2004; 27(suppl 1):S91-S93.
8. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233-240.
9. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med*. 2004;25:2147-2155.
10. Lawes CM, Parag V, Bennett DA, et al. Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care*. 2004;27: 2836-2842.
11. Gerstein HC. Glycosylated hemoglobin: finally ready for prime time as a cardiovascular risk factor. *Ann Intern Med*. 2004;141:475-476.
12. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141:413-420.
13. Kowalska I, Prokop J, Bachorzewska-Gajewska H, et al. Disturbances of glucose metabolism in men referred for coronary arteriography. Postload glycemia as predictor for coronary atherosclerosis. *Diabetes Care*. 2001;24:897-901.
14. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;359:2140-2144.
15. Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. *J Am Coll Cardiol*. 1999;33:612-619.
16. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773-778.
17. Foo K, Cooper J, Deaner A, et al. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart*. 2003;89:512-516.
18. Sala J, Masia R, Gonzalez de Molina FJ, et al. Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission. *J Epidemiol Community Health*. 2002;56:707-712.
19. Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care*. 1999;22:1827-1831.
20. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ*. 1997;314:1303-1306.
21. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol*. 2004;24:816-823.
22. Stern MP. Diabetes and cardiovascular disease: the "common soil" hypothesis. *Diabetes*. 1995;44:369-374.
23. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414:813-820.
24. Han I, Kudlow JE. Reduced O glycosylation of Sp1 is associated with increased proteasome susceptibility. *Mol Cell Biol*. 1997;17:2550-2558.
25. Han I, Oh ES, Kudlow JE. Responsiveness of the state of O-linked N-acetylglucosamine modification of nuclear pore protein p62 to the extracellular glucose concentration. *Biochem J*. 2000;350:109-114.
26. Du XL, Edelstein D, Dimmeler S, et al. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *J Clin Invest*. 2001;108:1341-1348.

Main Points

- The incidence of cardiovascular disease (CVD) in men and women with diabetes mellitus is up to 3 to 4 times higher than in unaffected individuals.
- Typical measurements of glycemia, including fasting plasma glucose, 2-hour plasma glucose, and glycated hemoglobin (A_{1c}, which correlates with mean glucose levels over the previous 2 to 3 months), are all associated with CVD, in a progressive relationship that extends to individuals with glucose abnormalities that are close to the normal range.
- Three related explanations may account for the link between elevated glucose levels and CVD: a direct effect of elevated glucose levels; a decreased insulin effect due to reduced insulin secretion, reduced insulin action (ie, insulin resistance), or a combination of these abnormalities; and an underlying genetic and/or environmental abnormality that predisposes individuals to both diabetes and CVD.
- Some of the mechanisms by which high blood pressure may contribute to vascular disease include increased sympathetic drive, endothelial dysfunction, generation of oxygen free radicals, inflammation of the vessel wall, and left ventricular hypertrophy—all of which are at least partially mediated by the renin-angiotensin system.
- Whether glucose lowering (by increasing the insulin effect) has cardiovascular benefit is an actively researched question with some positive supporting data.

27. James LR, Fantus IG, Goldberg H, et al. Overexpression of GFAT activates PAI-1 promoter in mesangial cells. *Am J Physiol Renal Physiol*. 2000;279:F718-F727.
28. Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci U S A*. 2000;97: 12222-12226.
29. Werstuck GH, Khan MI, Femia G, et al. Glucosamine-induced endoplasmic reticulum dysfunction is associated with accelerated atherosclerosis in a hyperglycemic mouse model. *Diabetes*. 2006;55:93-101.
30. Kim AJ, Shi Y, Austin RC, Werstuck GH. Valproate protects cells from ER stress-induced lipid accumulation and apoptosis by inhibiting glycogen synthase kinase-3. *J Cell Sci*. 2005; 118:89-99.
31. Jiang HY, Wek SA, McGrath BC, et al. Phosphorylation of the alpha subunit of eukaryotic initiation factor 2 is required for activation of NF-kappaB in response to diverse cellular stresses. *Mol Cell Biol*. 2003;23:5651-5663.
32. Hossain GS, van Thienen JV, Werstuck GH, et al. TDAG51 is induced by homocysteine, promotes detachment-mediated programmed cell death, and contributes to the development of atherosclerosis in hyperhomocysteinemia. *J Biol Chem*. 2003;278:30317-30327.
33. Robertson RP, Harmon J, Tran PO, et al. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes*. 2003;52:581-587.
34. Stumvoll M, Tataranni PA, Stefan N, et al. Glucose allostasis. *Diabetes*. 2003;52:903-909.
35. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201-229.
36. Dubois M, Kerr-Conte J, Gmyr V, et al. Nonesterified fatty acids are deleterious for human pancreatic islet function at physiological glucose concentration. *Diabetologia*. 2004;47:463-469.
37. Diaz R. Metabolic modulation of acute myocardial infarction. *Crit Care Clin*. 2001;17:469-476.
38. Lopaschuk GD. Metabolic abnormalities in the diabetic heart. *Heart Fail Rev.* 2002;7:149-159.
39. Wolff AA, Rotmensch HH, Stanley WC, Ferrari R. Metabolic approaches to the treatment of ischemic heart disease: the clinicians' perspective. *Heart Fail Rev*. 2002;7:187-203.
40. Das UN. Is insulin an endogenous cardioprotector? *Crit Care*. 2002;6:389-393.
41. Hansen TK, Thiel S, Wouters PJ, et al. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab*. 2003;88:1082-1088.
42. Das UN. Insulin: an endogenous cardioprotector. *Curr Opin Crit Care*. 2003;9:375-383.
43. Vehkavaara S, Makimattila S, Schlenzka A, et al. Insulin therapy improves endothelial function in type 2 diabetes. *Arterioscler Thromb Vasc Biol*. 2000;20:545-550.
44. Longnecker MP, Daniels JL. Environmental contaminants as etiologic factors for diabetes. *Environ Health Perspect*. 2001;109(suppl 6):871-876.
45. Kapaj S, Peterson H, Liber K, Bhattacharya P. Human health effects from chronic arsenic poisoning—a review. *J Environ Sci Health A Tox Hazard Subst Environ Eng*. 2006;41:2399-2428.
46. Schwartz GG, Il'yasova D, Ivanova A. Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. *Diabetes Care*. 2003;26:468-470.
47. Prozialeck WC, Edwards JR, Woods JM. The vascular endothelium as a target of cadmium toxicity. *Life Sci*. 2006;79:1493-1506.
48. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345:790-797.
49. Fantuzzi G, Mazzone T. Adipose tissue and atherosclerosis: exploring the connection. *Arterioscler Thromb Vasc Biol*. 2007;27:996-1003.
50. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J*. 2007;153:907-917.
51. Meek SE, Nair KS, Jensen MD. Insulin regulation of regional free fatty acid metabolism. *Diabetes*. 1999;48:10-14.
52. Gastaldelli A, Miyazaki Y, Pettiti M, et al. Metabolic effects of visceral fat accumulation in type 2 diabetes. *J Clin Endocrinol Metab*. 2002;87:5098-5103.
53. Lee Y, Hirose H, Ohneda M, et al. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A*. 1994;91:10878-10882.
54. Katsuki A, Sumida Y, Murashima S, et al. Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1998;83:859-862.
55. Daimon M, Oizumi T, Saitoh T, et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population: the Funagata study. *Diabetes Care*. 2003;26:2015-2020.
56. de Rekeneire N, Peila R, Ding J, et al. Diabetes, hyperglycemia, and inflammation in older individuals: the health, aging and body composition study. *Diabetes Care*. 2006;29:1902-1908.
57. Motoshima H, Wu X, Sinha MK, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab*. 2002;87:5662-5667.
58. Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet*. 2002;360:57-58.
59. Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. *Lancet*. 2003;361:226-228.
60. Maahs DM, Ogden LG, Kinney GL, et al. Low plasma adiponectin levels predict progression of coronary artery calcification. *Circulation*. 2005;111:747-753.
61. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J*. 2006;27:713-721.
62. Pechere-Bertschi A, Greminger P, Hess L, et al. Swiss Hypertension and Risk Factor Program (SHARP): cardiovascular risk factors management in patients with type 2 diabetes in Switzerland. *Blood Press*. 2005;14:337-344.
63. Selby JV, Peng T, Karter AJ, et al. High rates of co-occurrence of hypertension, elevated low-density lipoprotein cholesterol, and diabetes mellitus in a large managed care population. *Am J Manag Care*. 2004;10:163-170.
64. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*. 2000;342:905-912.
65. Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2006; 166:2191-2201.
66. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913.
67. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia*. 1998;41:127-133.
68. Ferrannini E, Seghieri G, Muscelli E. Insulin and the renin-angiotensin-aldosterone system: influence of ACE inhibition. *J Cardiovasc Pharmacol*. 1994;24(suppl 3):S61-S69.
69. Esler M. Differentiation in the effects of the angiotensin II receptor blocker class on autonomic function. *J Hypertens Suppl*. 2002;20:S13-S19.
70. Torlone E, Rambotti AM, Perriello G, et al. ACE-inhibition increases hepatic and extrahepatic sensitivity to insulin in patients with type 2 (non-insulin-dependent) diabetes mellitus and arterial hypertension. *Diabetologia*. 1991;34: 119-125.
71. Gillespie EL, White CM, Kardas M, et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care*. 2005;28:2261-2266.
72. Bosch J, Yusuf S, Gerstein HC, et al. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355:1551-1562.
73. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet*. 2007;369:1208-1219.
74. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure–lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005;165:1410-1419.
75. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000;355:253-259.
76. Lee M, Aronne LJ. Weight management for type 2 diabetes mellitus: global cardiovascular risk reduction. *Am J Cardiol*. 2007;99:68B-79B.
77. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;357:905-910.
78. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular

events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849-1861.
79. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;22:2643-2653.
80. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
81. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279-1289.
82. Buse JB, Rosenstock J. Prevention of cardiovascular outcomes in type 2 diabetes mellitus: trials on the horizon. *Endocrinol Metab Clin North Am*. 2005;34:221-235.
83. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158.
84. Knopp RH, d'Emden M, Smilde JG, Pocock SJ; the ASPEN Study Group. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes. *Diabetes Care*. 2006;29:1478-1485.
85. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.
86. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
87. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.
88. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.
89. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995-1003.
90. Viberti G, Kahn SE, Greene DA, et al. A Diabetes Outcome Progression Trial (ADOPT). An international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care*. 2002;25:1737-1743.
91. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
92. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996; 335:1001-1009.
93. Keech A, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care*. 2003;26:2713-2721.