Myocardial Glucose Transport and Utilization: A Target for Therapeutic Intervention

Premranjan P. Singh, MD, Rodrigo M. Lago, MD,
Richard W. Nesto, MD, FACC

Harvard Medical School, Boston, MA and Lahey Clinic Medical Center, Burlington, MA

Patients with type 2 diabetes mellitus (T2DM) have a 2-fold to 4-fold greater risk of cardiovascular mortality than nondiabetic individuals. The overall mortality rate of patients with T2DM is approximately twice that of people without diabetes. The excess in-hospital mortality of these patients is primarily due to an increased risk of congestive heart failure. Reduced compensatory ability of the noninfarcted myocardium and an underlying abnormality in the myocardial substrate metabolism (referable to the diabetic state) may also contribute to poor outcomes. Insulin resistance (IR) is a significant predictor of cardiovascular mortality and morbidity across a spectrum of glucose tolerance. Cardiac mass increases across the range of IR in subjects without diabetes, as well as across the range of glucose intolerance in subjects with diabetes. In one study, elevated fasting plasma glucose was an independent predictor of hospitalization for heart failure. Optimization of cardiac metabolism could become a new target for therapeutic intervention in patients with ischemic heart disease and diabetes.

[Rev Cardiovasc Med. *2008;9(2):106-110*]

Key words: Diabetes mellitus • Cardiovascular disease • Insulin resistance • Glucose tolerance

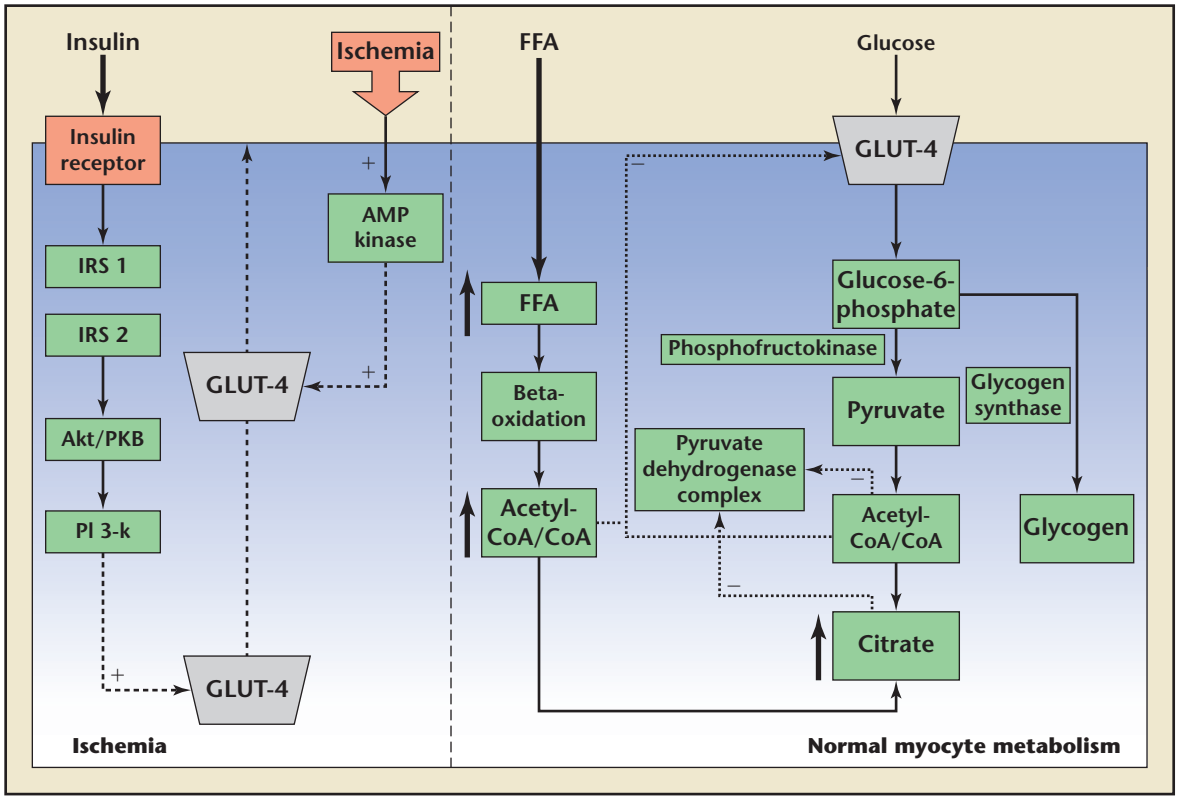
The incidence and prevalence of type 2 diabetes mellitus (T2DM) are increasing. It is projected that the number of people with diabetes will rise from 171 million in 2000 to 366 million by 2030.[1] Patients with T2DM have a 2-fold to 4-fold greater risk of cardiovascular mortality than nondiabetic individuals. Despite significant progress in the treatment of acute coronary syndromes, the overall mortality rate of patients with T2DM is still approximately twice that of people without diabetes.

The excess in-hospital mortality of these patients is primarily due to an increased risk of congestive heart failure. Several other mechanisms may also play a role. It has been suggested that the reduced compensatory ability of the noninfarcted myocardium and an underlying abnormality in the myocardial substrate metabolism (referable to the diabetic state) may also contribute to poor outcomes.[2] Another reason for the increase in congestive heart failure in T2DM patients is their greater risk of developing diastolic dysfunction.

In healthy people, the primary sources of myocardial energy are free fatty acids (FFAs) in the fasting state and glucose in the fed state.[3] During ischemia, myocyte survival is more dependent on glucose-derived generation of high-energy phosphates because there is a shift towards anaerobic metabolism as a critical adaptive mechanism. Glucose uptake can be stimulated by insulin in dysfunctional myocardium.[4] At the cellular level, members of the glucose transporters (GLUT) family facilitate myocardial glucose uptake. The most important GLUT, GLUT4, is translocated from the cytosol to the plasma membrane by insulin stimulation, increased myocardial work, and ischemia (Figure 1).[5,6]

It is now well established that T2DM, which is characteristically diagnosed by hyperglycemia, is a progressive disorder caused by a combination of insulin resistance (IR)—in the skeletal muscle, adipose tissue, and liver—and impaired insulin secretion by pancreatic β-cells. IR is a mechanism underlying impaired glucose tolerance and T2DM, and it increases cardiovascular risk.[7] In the Botnia study, IR was found to be a

Figure 1. *Glucose and FFA metabolism in the heart. Transmembrane glucose transport by the insulin-sensitive transporter GLUT4 accelerates both mitochondrial oxidation of glucose-derived acetyl coenzyme A and glycogen accumulation by glycolysis, glucose oxidation (pyruvate dehydrogenase complex), and glycogen synthesis (glycogen synthase). Increased myocardial uptake and oxidation of exogenous FFA increase the cytosolic acetyl-CoA/CoA ratio and citrate concentration, which in turn inhibit pyruvate dehydrogenase complex, phosphofructokinase, and glucose transport. During ischemia, there is an independent increase in myocardial glucose uptake. Insulin promotes translocation of GLUT4 from an intracellular storage compartment to the plasma membrane through receptor-stimulated activation of a phosphorylation cascade involving IRS-1 and IRS-2 and the protein kinases Akt/PKB and PI 3-k. The ischemic signal results in GLUT4 translocation as a consequence of reduced cellular energy charge activating the AMP-sensitive protein kinase. Subsequent glucose uptake increases cardiomyocyte adenosine triphosphate formation by increasing glucose flux through glycolysis and the pyruvate dehydrogenase complex resulting in glucose oxidation. FFA, free fatty acid; GLUT, glucose transporters; IRS, insulin receptor substrates; AMP, adenosine monophosphate; Akt/PKB, Akt/protein kinase B; PI 3-k, phosphoinositide 3-kinase.* www.medreviews.com



significant predictor of cardiovascular mortality and morbidity across a spectrum of glucose tolerance.[8]

Rutter and colleagues[9] have shown that cardiac mass increases across the range of IR in subjects without diabetes, as well as across the range of glucose intolerance in subjects with diabetes. In a clinical trial cohort of 31,546 subjects, Held and colleagues[10] found that elevated fasting plasma glucose was an independent predictor of hospitalization for heart failure. A similar finding was observed by Ingelsson and coworkers,[11] who demonstrated the central role of IR in predicting coronary heart failure in elderly men independent of other established risk factors for it.

Whole body and skeletal muscle IR is common in the patient with T2DM, but data regarding myocardial IR are limited and controversial. Dutka and associates[12] investigated the combined effect of T2DM and ischemic systolic dysfunction on myocardial glucose utilization using fluorodeoxyglucose and positron emission tomography (FDG-PET) and GLUT4 distribution. This single-center study included 54 patients (19 with T2DM and 35 without T2DM) with heart failure secondary to coronary artery disease who had myocardial viability assessments prior to coronary artery bypass grafting (CABG). Patients with recent myocardial infarction, unstable angina, decompensated congestive heart failure, and insulin-treated diabetes were excluded. Age, body mass index, heart rate, left ventricular ejection fraction, and blood pressure were similar in both groups. A hyperinsulinemic clamp was used to determine whole body insulin sensitivity and myocardial glucose utilization. In a subgroup of 18 patients (6 with T2DM), biopsy was obtained during CABG to assess GLUT4 distribution. Patients with diabetes had a significantly higher fasting plasma glucose than patients without diabetes (8.0 +/− 3.6 vs 5.0 +/− 0.6 mmol/L; $P < .001$) and significantly higher fasting plasma insulin (66 +/− 76 vs 33 +/− 34 mmol/L; $P < .001$). During use of the hyperinsulinemic glucose clamp, myocardial glucose utilization (measured using FDG) was significantly lower in patients with diabetes than in patients without diabetes (0.34 +/− 0.16 vs 0.47 +/− 0.24 micro mol/min; $P = .0002$). Despite higher blood glucose concentration and comparable plasma insulin concentration, myocardial glucose utilization was significantly lower in diabetic patients than nondiabetic patients, indicating the presence of myocardial IR. Myocardial blood flow was similar in both groups, but myocardial glucose extraction was significantly reduced in the patients with diabetes than without (7.1 +/− 3.1% vs 13.5 +/− 5.2%; $P < .01$).

The myocardial amount of GLUT4 was significantly lower in the patients with heart failure than it was in samples from healthy donor hearts. However, GLUT4 expression was similar in patients with and without diabetes, suggesting that GLUT4 expression is not a specific limiting factor for myocardial glucose utilization in the setting of diabetes. Lower glucose utilization in T2DM instead may be partly explained by the higher concentration of FFA, which activates pathways that lead to the attenuation of the insulin signal, as suggested in this study. Altered metabolism and impaired insulin action in the heart are both cause and consequence of altered cardiac function and are likely to be multifactorial.

Clinical trials have tested the hypothesis that insulin administration during acute myocardial infarction may improve clinical outcome. The presumed mechanism behind this benefit of insulin infusion is the decrease in blood glucose and FFA, each of which affects myocardial metabolism, myocardial function, microvascular blood flow, oxidative stress, and inflammation.[13,14]

Optimization of cardiac metabolism could become a new target for therapeutic intervention in patients with ischemic heart disease and diabetes (Figure 2). Manipulations of metabolic substrate are intended to shift the ischemic myocardium from FFA to glucose utilization.[15] Studies conducted in isolated perfused hearts confirm that a switch from FFA to glucose as the metabolic substrate for energy production can exert favorable effects on the diabetic heart.[15]

In a single-center, randomized, controlled, prospective trial among 1548 surgical intensive care patients receiving mechanical ventilation, Van den Berghe and colleagues[16,17] demonstrated that treated patients had a 34% reduction in mortality and a 40% to 50% reduction in important comorbidities compared with untreated patients. The therapeutic goal in the treated group was maintenance of euglycemia at 80 to 110 mg/dL using a continuous intravenous infusion of insulin. Similarly, researchers using the Portland Protocol, in which diabetic patients undergoing cardiovascular surgery receive intensive glycemic management with continuous intravenous insulin infusion, have demonstrated that glycemic control is strongly associated with reductions in mortality and incidence of deep sternal wound infections.[18]

In animal models, rosiglitazone (a peroxisome proliferator-activated receptor γ [PPARγ] agonist) increased the concentrations of GLUT1 and GLUT4 and restored myocardial

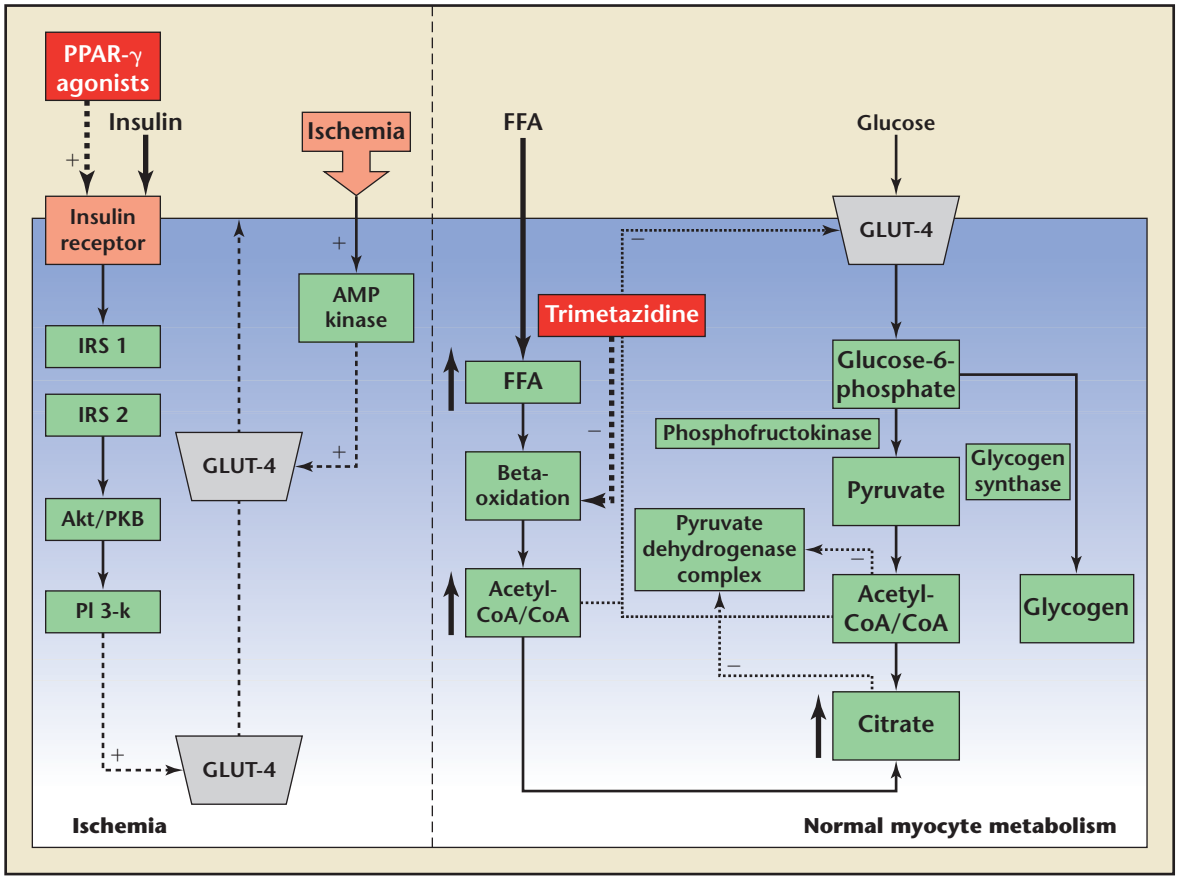


Figure 2. *Therapeutic interventions targeting myocardial metabolism. PPARγ agonists and trimetazidine are examples of agents that switch substrate oxidation away from fatty acids and toward carbohydrate oxidation. PPARγ, peroxisome proliferator-activated receptor γ; FFA, free fatty acid; GLUT, glucose transporters; IRS, insulin receptor substrates; AMP, adenosine monophosphate; Akt/PKB, Akt/protein kinase B; PI 3-k, phosphoinositide 3-kinase.* www.medreviews.com

glucose uptake during ischemia, thus protecting myocardium from ischemic injury.[19] In a human study, Lautamäki and associates[20] demonstrated that rosiglitazone therapy significantly increased insulin sensitivity and improved myocardial glucose uptake in type 2 diabetes patients with coronary artery disease, but that it had a limited role in patients with heart failure. Trimetazidine, an anti-ischemic metabolic agent, improves

Main Points

- Insulin resistance (IR) was found to be a significant predictor of cardiovascular mortality and morbidity across a spectrum of glucose tolerance.
- Whole body and skeletal muscle IR is common in the patient with T2DM, but data regarding myocardial IR are limited and controversial.
- Optimization of cardiac metabolism could become a new target for therapeutic intervention in patients with ischemic heart disease and diabetes.
- Studies conducted in isolated perfused hearts confirm that a switch from free fatty acids to glucose as the metabolic substrate for energy production can exert favorable effects on the diabetic heart.
- In diabetic patients undergoing cardiovascular surgery who receive intensive glycemic management with continuous intravenous insulin infusion, glycemic control is strongly associated with reductions in mortality and incidence of deep sternal wound infections.

myocardial glucose utilization by inhibiting fatty acid oxidation, which is achieved by preventing the release of mitochondrial long-chain 3 ketoacyl coenzyme A thiolase and by shifting energy production from FFA to glucose oxidation—another example of a beneficial effect of optimizing cardiac metabolism in T2DM[21] (Figure 2). Similarly, ranolazine reduces calcium overload in the ischemic myocyte by inhibiting late sodium current and improving left ventricular performance in experimental models of heart failure.[22] The targeting of cardiac metabolism and myocardial IR deserves further investigation in clinical settings. ■

References

1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27:1047-1053.
2. Aronson D, Rayfield EJ, Chesebro JH. Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med*. 1997;126:296-306.
3. Camici P, Ferrannini E, Opie LH. Myocardial metabolism in ischemic heart disease: basic principles and application to imaging by positron emission tomography. *Prog Cardiovasc Dis*. 1989;32:217-238.
4. Maki M, Luotolahti M, Nuutila P, et al. Glucose uptake in the chronically dysfunctional but viable myocardium. *Circulation*. 1996;93:1658-1666.
5. Sun D, Nguyen N, DeGrado TR, et al. Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 to the plasma membrane of cardiac myocytes. *Circulation*. 1994;89:793-798.
6. Zaninetti D, Greco-Perotto R, Jeanrenaud B. Heart glucose transport and transporters in rat heart: regulation by insulin, workload and glucose. *Diabetologia*. 1988;31:108-113.
7. Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care*. 2002;25:1135-1141.
8. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683-689.
9. Rutter MK, Parise H, Benjamin EJ, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation*. 2003;107:448-454.
10. Held HC, Gerstein S, Yusuf F, et al, for the ONTARGET/TRANSCEND Investigators. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. *Circulation*. 2007;115:1371-1375.
11. Ingelsson E, Sundstrom J, Arnlov J, et al. Insulin resistance and risk of congestive heart failure. *JAMA*. 2005;294:334-341.
12. Dutka DP, Pitt M, Pagano D, et al. Myocardial glucose transport and utilization in patients with type 2 diabetes mellitus, left ventricular dysfunction, and coronary artery disease. *J Am Coll Cardiol*. 2006;48:2225-2231.
13. Malmberg K, Ryden L, Efendic S, Welin L. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57-65.
14. Chaudhuri A, Janicke D, Wilson MF, Dandona P. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment-elevation myocardial infarction. *Circulation*. 2004;109:849-854.
15. Marzilli M. Management of ischaemic heart disease in diabetic patients. Is there a role for cardiac metabolic agents? *Curr Med Res Opin*. 2001;17:153-158.
16. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
17. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359-366.
18. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:1007-1021.
19. Sidell RJ, Cole MA, Draper NJ, et al. Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the Zucker fatty rat heart. *Diabetes*. 2002;51:1110-1117.
20. Lautamäki R, Airaksinen KE, Seppänen M, et al. Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind, placebo-controlled study. *Diabetes*. 2005;54:2787-2794.
21. Fantini E, Demaison L, Sentex E, et al. Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. *J Mol Cell Cardiol*. 1994;26:949-958.
22. Chandler MP, Stanley WC, Morita H, et al. Short-term treatment with ranolazine improves mechanical efficacy in dogs with chronic heart failure. *Circ Res*. 2002;91:278-280.