Identifying Appropriate Patients With Insulin Resistance Syndrome and Effective Management Strategies for Optimal Outcomes

Richard W. Nesto, MD, FACC

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Department of Cardiovascular Medicine, Lahey Clinic Medical Center, Burlington, MA

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Type 2 diabetes is one of the most common diseases in the world. It is expected that the prevalence of type 2 diabetes worldwide will increase from its current level of 150 million people to 225 million by 2010 and to 300 million by 2025. However, these figures represent only clinically diagnosed diabetes. Many additional cases remain undiagnosed and untreated, and as many as 25% of people in western countries have impaired glucose tolerance (IGT), a condition which sets the stage for type 2 diabetes.[1] Diabetes has high long-term morbidity and mortality, primarily due to associated microvascular and macrovascular complications,[2,3] and a large body of evidence indicates that insulin resistance plays a primary role in the development of type 2 diabetes.[4] Even before the appearance of hyperglycemia, patients often have insulin resistance and a number of other physiologic abnormalities that significantly increase cardiovascular risk, including hypertension, atherogenic dyslipidemia, a prothrombotic environment, and significant vascular and hemodynamic abnormalities that result from endothelial cell dysfunction.[5,6] This constellation of abnormalities is often referred to as the insulin resistance syndrome (IRS) or metabolic syndrome, and it is now recognized as an important target for therapeutic intervention to decrease cardiovascular risk.[7]

The mechanisms by which the IRS increases cardiovascular risk are not completely understood, but a growing body of evidence indicates that effects of this metabolic abnormality on the vascular endothelium may play a central role in this process. The vascular endothelium is a highly active metabolic and endocrine organ that produces a large number of different molecules regulating vasoconstriction, vasodilation, coagulation, and cellular proliferation, events that play key roles in the development of atherosclerosis and cardiovascular disease.[8] The IRS may be linked to endothelial dysfunction via many different pathways, all of which have implications for management of patients at risk for development of cardiovascular disease.[6]

Management of the patient with IRS must take into account all of the factors comprising this condition in order to effectively decrease cardiovascular risk. Pharmacotherapy aimed at correcting dyslipidemia and lowering blood pressure have been shown to decrease cardiovascular events, but results with therapy aimed at achieving glycemic control in patients with overt diabetes have been more variable. The thiazolidinediones (TZDs) may be particularly appropriate as a component of therapy for cardiovascular risk reduction in patients with type 2 diabetes. These drugs bind to peroxisome proliferator-activated receptors (PPARs) and have been shown to have positive effects on several cardiovascular risk factors associated with IRS. It has even been suggested that these drugs may prevent the progression of insulin resistance to diabetes and of endothelial dysfunction to atherosclerosis.[9]

This supplement issue of *Reviews in Cardiovascular Medicine* focuses on the importance of insulin resistance in the pathogenesis of type 2 diabetes, the relationship between IRS and cardiovascular disease, and how best to manage patients with these conditions to correct metabolic abnormalities and decrease cardiovascular risk. Dr. Barry J. Goldstein reviews the progression from insulin resistance to overt type 2 diabetes with emphasis on the adverse metabolic effects of adiposity and the manner in which changes in endothelial function associated with insulin resistance may contribute to the development of hypertension and atherosclerosis. My own article follows with a review of additional evidence supporting the link between IRS and cardiovascular disease, as well as treatment strategies for patients with diabetes aimed at decreasing cardiovascular risk. IGT is a risk factor for development of both diabetes and cardiovascular disease, and therapies aimed at reducing insulin resistance and correcting IGT may be more successful than traditional strategies in delaying diabetes progression and decreasing cardiovascular risk.

Dr. Stuart W. Zarich's review emphasizes the importance of comprehensive therapy with strict glycemic control, accompanied by additional proven antihypertensive and lipid-lowering therapies and lifestyle modification to decrease cardiovascular risk.

Dr. Stephen Edelman provides a detailed review of TZDs. Studies with these agents, often referred to as insulin sensitizers, suggest that they have the potential to alter the natural history of diabetes. Long-term treatment with TZDs does not appear to be limited by the secondary failure often seen with other oral antidiabetic drugs, and they may be particularly useful as first-line early treatment for patients with diabetes as well as those at high risk for this disease.

Dr. Gregg C. Fonarow emphasizes the point that diabetes substantially increases the risk of mortality after acute coronary syndromes, and that the neurohormonal systems of patients with diabetes and cardiovascular events play a key role in disease progression. Pharmacologic intervention in these patients should focus on blocking the deleterious effects of the renin-angiotensin-aldosterone system as well as the sympathetic nervous system. Treatment with a ß-blocker and an angiotensin converting enzyme inhibitor should be standard therapy for all patients with diabetes and cardiovascular disease.

Drs. Ankur Shah and Richard P. Shannon extend analysis of the relationship between insulin resistance and cardiovascular disease to dilated cardiomyopathy. It is generally accepted that IRS can lead indirectly to the development of cardiomyopathy, and results from recent studies provide support for the view that cardiomyopathy can result in insulin resistance at both a whole body and a myocardial level. Myocardial insulin resistance has particularly important implications for the failing heart because of its preference for glucose oxidation.

This supplement will bring the reader up to date, with very recent information on the importance of insulin resistance in the pathogenesis of both type 2 diabetes and cardiovascular disease, new approaches to treatment, and ways to integrate therapy for comprehensive management of patients at high risk for cardiovascular morbidity and mortality. ■

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