The Relation of Insulin Resistance Syndromes to Risk of Cardiovascular Disease

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Diabetes mellitus is one of the most common problems challenging physicians in the 21st century. Type 2 diabetes mellitus accounts for at least 90% of all cases, which can be attributed in part to an aging population and the prevalence of obesity and sedentary lifestyles. In addition to the major impact on quality of life, diabetes accounts for a significant proportion of global healthcare expenditure, with the majority of costs attributable to treatment of its long-term complications. The principal cause of diabetes mortality is cardiovascular disease (CVD). There is a long period, prior to clinical detection of the disease, in which insulin resistance and hyperglycemia gradually worsen, and vascular complications develop. This article reviews the relationship between diabetes and the risk of CVD.
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Key words: Diabetes mellitus • Cardiovascular disease • Insulin resistance

Diabetes mellitus is one of the most common problems challenging physicians in the 21st century. Around 140 million people worldwide currently have diabetes, with the number projected to reach 300 million by 2025.[1] Type 2 diabetes mellitus accounts for at least 90% of all cases, and the predicted explosion in the number of cases can be attributed in part to an aging population and the increasing prevalence of obesity and sedentary lifestyles. In

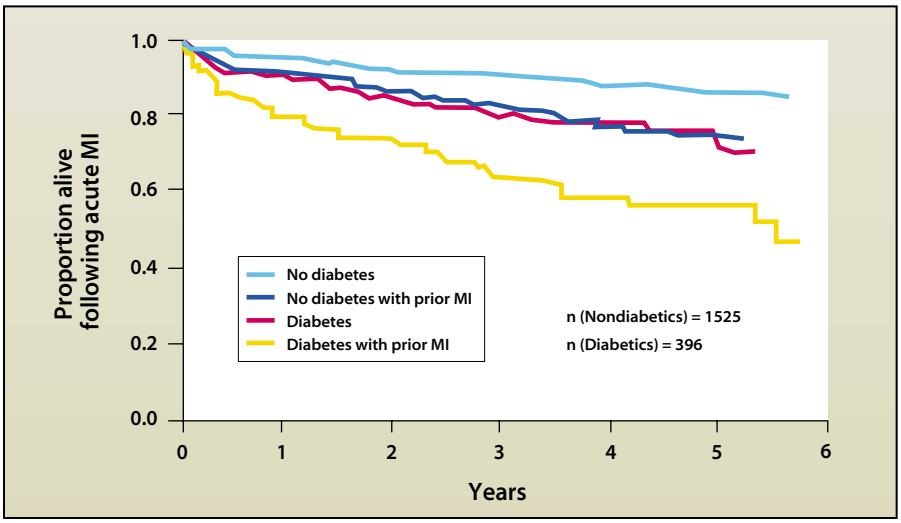

Figure 1. *Effect of diabetes on long-term survival following acute myocardial infarction (MI). Patients with diabetes have a survival rate similar to nondiabetic survivors of a previous MI. Reproduced with permission from Mukamal et al.*[6]

addition to the major impact on quality of life, diabetes accounts for a significant proportion of global healthcare expenditure, with the majority of costs attributable to treatment of its long-term complications, both macrovascular and microvascular. For example, whereas the prevalence of diabetes in the U.S. population was found to be 4.5% in 1992, diabetes accounted for 14.6% of total U.S. healthcare expenditure over the same period.[2] Subsequent reports highlight the major contribution of chronic complications, in particular, cardiovascular and renal disease, to these costs.[3]

The principal cause of diabetes morbidity and mortality is cardiovascular disease (CVD). Individuals with type 2 diabetes have a 2- to 4-fold increased risk of developing coronary heart disease compared with their counterparts without diabetes.[4,5] In a prospective cohort study involving almost 2000 patients (the Determinants of Myocardial Infarction Onset Study), diabetes was associated with a nearly 2-fold higher long-term mortality following acute myocardial infarction (Figure 1).[6] Even after adjustment for all other risk factors, type 2 diabetes remains a significant risk factor for coronary, cerebral, and peripheral vascular disease. A recent Finnish study reported that a person with diabetes who had not experienced a prior myocardial infarction had the same risk of a first myocardial infarction as did nondiabetic survivors of a myocardial infarction (Figure 2).[7] Although this influential study led the National Cholesterol Education Program Adult Treatment Panel III (ATP III) to treat diabetes as CVD risk equivalent,[8] others have disputed the impact of diabetes. A recent cross-sectional study of the Tayside, Scotland population reported fewer hospital admissions for myocardial infarction in the diabetic group without prior myocardial infarction than in the group who had experienced a prior myocardial infarction during the 7-year follow-up (risk ratio for prior myocardial infarction, 2.27, 95% CI, 1.82–2.83).[9] Similar observations were made in the accompanying cohort study, in which death from cardiovascular causes was nearly 3 times as frequent in the nondiabetic, prior myocardial infarction group. In the Multiple Risk Factor Intervention Trial (MRFIT), cardiovascular mortality was 5 times higher in men with diabetes (but no other risk factors) than in those without the condition.[10]

The severity and extent of macrovascular disease is also greater in patients with diabetes, and this has been shown in autopsy reports and studies of patients undergoing primary angioplasty. For example, in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study, patients with diabetes had a higher incidence of multivessel disease and a greater number of diseased vessel segments than diabetes-free individuals.[11] It is now well established that type 2 diabetes, which is characteristically diagnosed by hyperglycemia, is a progressive disorder caused by a combination of insulin resistance in skeletal muscle, adipose tissue, and liver, and impaired insulin secretion by pancreatic ß cells. There is generally a long period of asymptomatic diabetes, prior to clinical detection of the disease, during which insulin resistance and hyperglycemia worsen, and microvascular and macrovascular complications develop. This dysglycemic state, known as impaired glucose tolerance (IGT), is a risk factor

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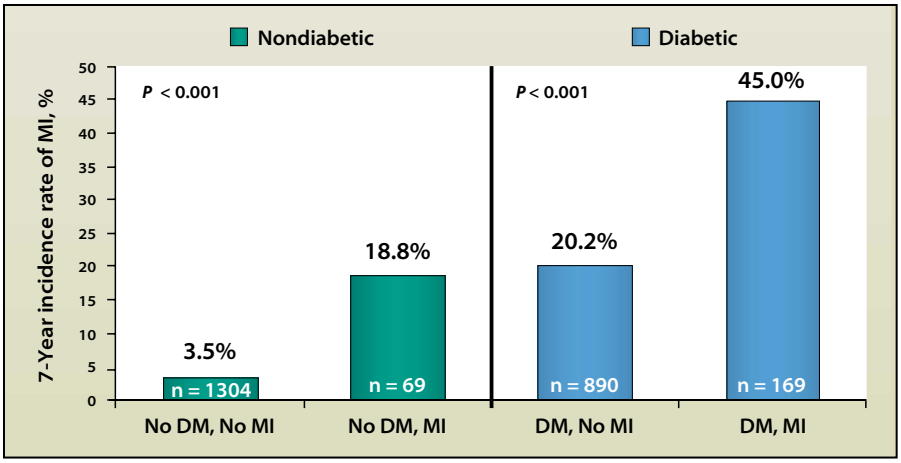


Figure 2. *Comparison of cardiovascular prognosis between individuals with and without diabetes mellitus (DM). Individuals with diabetes but no history of myocardial infarction (MI) have a similar rate of risk for MI as nondiabetic individuals with a prior MI. Reproduced with permission from Haffner et al.*[7]

for the development of both type 2 diabetes and CVD (Figure 3).

Aggregation of Traditional Coronary Heart Disease Risk Factors in Diabetes

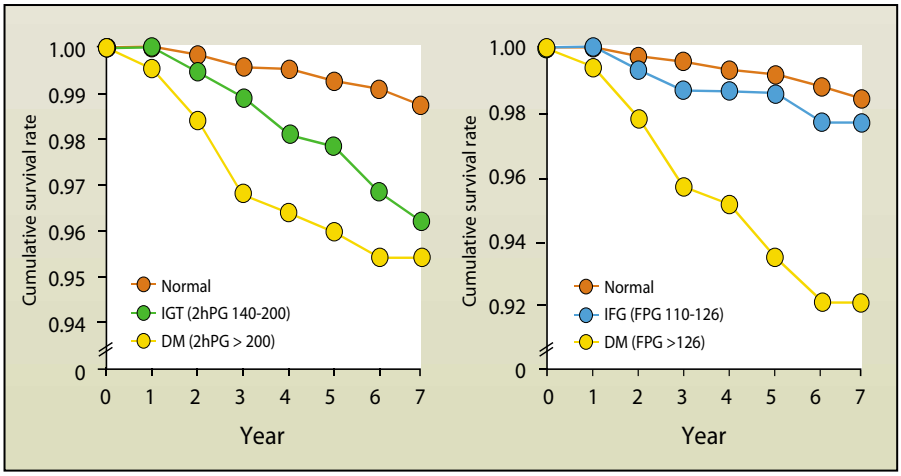
The high prevalence of established risk factors for coronary heart disease (CHD) in people with diabetes complicates the epidemiological assessment of CHD in this patient population.[12] CHD risk factors such as hypertension, dyslipidemia, and overweight and obesity cluster in patients with diabetes.[13] At the time of diagnosis, 50% of type 2 diabetic patients have hypertension and 30% have a dyslipidemia. In MRFIT, the classic risk factors known to predict CVD mortality in nondiabetic people—high serum cholesterol (≥ 200 mg/dL), elevated systolic blood pressure (≥ 120 mm Hg), and cigarette smoking—independently predicted CVD mortality in diabetic subjects.[10] Most men in either the diabetic or the nondiabetic group had one or more of these risk factors, with the majority having two or more. With each stratum of risk (none, one only, two only, or all three), CVD mortality was substantially higher for men with diabetes than for men without diabetes. Notably, there was a synergistic effect among diabetes and other risk factors such that the presence of any single risk factor or the combination of any two or all three was associated with a steeper increase in CVD mortality in men with diabetes than in those without the disease.

Plasma Glucose as an Independent Risk Factor for Coronary Heart Disease

Although diabetes clusters with the group of traditional risk factors for CHD mentioned above, the rate of CHD morbidity and mortality in diabetes exceeds the rate expected from the interaction of these multiple risk factors by approximately 50%. Hyperglycemia itself has emerged as a leading candidate responsible for the excess CHD risk in diabetes.

Compelling data have emerged from prospective observations of patients with type 2 diabetes in which patients were stratified by fasting plasma glucose (FPG) levels. In one such study, the average FPG level independently related to all-cause (P = .0002), cardiovascular (P = .0006), and ischemic heart disease (P = 0.03) mortality.[14] Similar results were reported in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study.[15] Over 29,000 men and women without a previous history of diabetes were followed for an average of 11 years. The highest incidence of all-cause, CVD, and non-CVD mortality was seen in subjects with the highest FPG. In the U.K. Prospective Diabetes Study (UKPDS), glycosylated hemoglobin (HbA_{1c}), a measure of chronic plasma glucose

Figure 3. *Cumulative cardiovascular survival data from the Funagata Diabetes Study. Impaired glucose tolerance (IGT) carries a cardiovascular prognosis that approximates type 2 diabetes. DM, diabetes mellitus; FPG, fasting plasma glucose; IFG, impaired fasting glucose; PM, plasma glucose. Reproduced with permission from Tominaga et al.*[33]



levels, was measured in 4585 type 2 diabetic patients who were followed for an average of 10 years.[16] Each 1% decrease in HbA_{1c} was associated with a 14% reduction in the incidence of fatal and nonfatal myocardial infarction ($P < .0001$). No threshold for FPG (or HbA_{1c}) above which there was a sharp increase in risk of CVD mortality was found in any of these studies. This continuous and graded association between FPG and CVD mortality has been reported in other ethnic groups, for example, Americans of Mexican descent.[17] In the San Antonio Heart Study, 4875 subjects (65% Americans of Mexican descent) were followed for 7 to 8 years. In subjects with type 2 diabetes (n = 471), those in the top quartile of FPG had a risk of CVD mortality 4.7 times greater than did subjects in quartiles 1 and 2 combined ($P = .01$). This increase in risk remained after adjustment for other potential risk factors.

Evidence points to a continuum of CHD risk that is dependent on glucose levels across the spectrum from normal glucose tolerance through impaired glucose tolerance to diabetes. Data from a cohort study performed in Rancho Bernardo, CA, showed that in both men and women, the prevalence of myocardial infarction and stroke correlated positively with glucose tolerance status.[18] Similar studies in diverse populations have also generally shown a graded relationship between glucose tolerance and the rate of CHD events.[19,20] Further indirect evidence for this continuum of risk is provided by the Nurses' Health Study, in which women who were diagnosed with type 2 diabetes during the 20-year follow-up had a nearly 4-fold increase in the risk of myocardial infarction in the period prior to diagnosis, compared with women who remained diabetes-free throughout the study.[21] Although not measured, it is likely that these subjects were glucose intolerant for some time prior to the diagnosis of diabetes.

Investigations into the relationship between glucose and CHD risk in the studies noted above have focused on CHD or ischemic mortality as the endpoint. Although powerful indicators of the graded and continuous effect of glucose, these studies provide no information on the effect of glucose on the vessel wall itself. Several studies have evaluated intima-media thickness (IMT) of the carotid artery by ultrasound in subjects with type 1 or type 2 diabetes.[22–24] Carotid IMT correlates well with cardiovascular risk factors and the occurrence of CHD in subjects with and without diabetes.[25] In the Atherosclerosis Risk in Communities (ARIC) Study, carotid wall thickness was correlated with fasting glucose tolerance in all gender and race subgroups in a large and diverse sample of 15,800 subjects without symptomatic CVD.

IGT Predisposes to Diabetes and CVD

IGT represents an intermediate metabolic stage between normal glucose homeostasis and diabetes, and, although individuals with IGT are often euglycemic in their daily lives, glucose intolerance is detected when the subject is challenged with an oral glucose tolerance test. The transition from normal glucose tolerance (NGT) through IGT to diabetes may be thought of as a continuum, in which the core defects of insulin resistance and ß cell dysfunction drive disease progression.[26] Not all subjects with IGT will go on to develop diabetes, but many individuals are at high risk of developing the condition.[27]

IGT as a Risk Factor for Type 2 Diabetes

IGT is a significant risk factor for progression to type 2 diabetes. In a group of Pima Indians defined as having IGT according to World Health Organization (WHO) criteria, the incidence of type 2 diabetes after 10 years follow-up was found to be 61%, compared with 7% in control subjects.[28] Similar figures have been reported from an analysis of 6 studies, involving a combined 2400 subjects with IGT, in which the annual diabetes conversion rate was found to be between 3.6% and 8.7%.[27] Furthermore, transient IGT has also been shown to predict the development of type 2 diabetes in Pima Indians.[29] In this study, individuals who had experienced a transient impairment of glucose tolerance had a higher 10-year incidence of type 2 diabetes when compared with control subjects (48% vs 8%, respectively).[29] Most recently, in the Hoorn study, the odds ratio for developing diabetes (according to WHO 1999 criteria) was 10.9 (95% CI, 6.0–19.9) in patients with IGT.[30] Of note, patients with both IGT and impaired fasting glucose (IFG) at baseline had an increased risk of developing diabetes (OR 39.5; 95% CI, 17.0–92.1).[30] Although the time interval between development of IGT and transition to type 2 diabetes may extend to 10 years or more,[31] it is important to emphasize that considerable macrovascular damage may be occurring during this period. Indeed, signs of macrovascular disease have been detected in 50% of patients with type 2 diabetes prior to diagnosis,[31]and it has been suggested that the state of IGT represents a period of enhanced cardiovascular risk, in which metabolic derangements initiate cardiovascular damage well before the onset of type 2 diabetes.[32]

IGT as a Risk Factor for CVD

A 7-year observational study correlating cause of death with glycemic

status in a cohort of over 2500 residents in Funagata, Japan, has highlighted the importance of IGT as a risk factor for CVD. At the end of this study, mortality rates from CVD (coronary heart disease and stroke) were significantly higher for individuals with IGT than for subjects with NGT.[33] Indeed, the significant negative impact of IGT on CVD could be seen in data taken only 4 years into the study. These findings reflect the fact that fasting hyperglycemia may not be the sole cause of macrovascular damage, because baseline fasting plasma glucose (FPG) levels were low in the IGT subjects (mean FPG at baseline: 99 ± 12 mg/dL or 5.5 ± 0.7 mmol/L).[33]

Findings from the Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes (RIAD) study support this proposal.[34] In this study, the relationship between hyperglycemia and carotid IMT, an indicator of atherosclerosis, was investigated in 785 patients at high risk of developing type 2 diabetes due to a family history of the condition. The results showed that, whereas there was a significant correlation between IMT and either 2 hours postchallenge glucose (2hPG) or FPG, 2hPG was found to correlate more closely with IMT than FPG ($r = 0.23$, $P < .001$ vs $r = 0.14$, $P < .004$, respectively).[34] A separate, large-scale, prospective population survey of over 2400 Japanese subjects has demonstrated that cardiovascular risk increases with a rising level of glucose intolerance.[35] In this study, the risk of CVD (stroke or coronary heart disease) increased with deterioration in glucose tolerance, such that subjects diagnosed at baseline with IGT or type 2 diabetes had a significantly increased risk (relative risks 1.9, 95% CI, 1.2–3.2 and 3.0, 95% CI, 1.8–5.2, respectively) compared with individuals with NGT.[35]

The Role of Insulin Resistance

What factors are responsible for this increase in cardiovascular risk? A common feature underlying IGT, type 2 diabetes, and CVD is insulin resistance, which is present in over 80% of patients with type 2 diabetes,[36] and has recently been confirmed as an independent risk factor for CVD.[37] Supportive evidence comes from a U.S. meta-analysis, which estimated that insulin resistance approximately doubles the annual risk of a coronary heart disease event, irrespective of the presence of type 2 diabetes.[38] Indeed, the authors of the Funagata study have suggested insulin resistance should be regarded, in parallel with hypertension and dyslipidemia, as a therapeutic target that requires intervention.[33]

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Both IGT and insulin resistance are components of a cluster of metabolic abnormalities that together constitute the insulin resistance syndrome (IRS) or metabolic syndrome, which has been linked with increased risk of cardiovascular mortality and morbidity. The WHO and U.S. National Cholesterol Education Program (NCEP) have published definitions of the syndrome, which accommodate traditional cardiovascular risk factors, including hyperglycemia, hypertension, dyslipidemia (elevated triglycerides and decreased high-density lipoprotein [HDL] cholesterol), and abdominal obesity.[39,40] However, there are a number of differences between these definitions: while WHO incorporates a direct measure of insulin resistance, NCEP guidelines include surrogate measures of insulin resistance that are more appropriate for clinical practice.

Evidence of the central role of insulin resistance in the development of IRS comes from the Bruneck Study,[36] which evaluated the prevalence of insulin resistance among 4800 subjects aged 40–79 years using the homeostasis model assessment (HOMA) method, a technique that allows both insulin resistance and ß cell function to be estimated from a single measure of fasting plasma insulin and glucose.[41] In this study, the degree of insulin resistance correlated with the number of metabolic abnormalities, and, where several abnormalities were clustered together, insulin resistance was almost always present. Moreover, in the San Antonio Heart Study, two subgroups of patients who developed type 2 diabetes during 7-year follow-up were observed: insulin-resistant converters and insulin-sensitive converters.[42] Of note, only the insulin-resistant converters showed pro-atherogenic profiles such as dyslipidemia and hypertension at baseline, while insulin-sensitive converters had a lipid and blood pressure profile comparable to subjects who did not develop diabetes.[42]

Additional support comes from the Botnia study, which estimated the cardiovascular risk associated with IRS using the WHO definition of the syndrome. In this study, IRS was found to be a significant predictor of cardiovascular mortality and morbidity across a spectrum of glu-

cose tolerance.[43] These observations suggest that the raised CVD risk associated with IGT and type 2 diabetes is intimately associated with insulin resistance. Thus, while substantial clinical benefits can be derived from reducing hyperglycemia in type 2 diabetes, reducing insulin resistance is likely to have additional benefits leading to a greater impact on the incidence of cardiovascular events. The increasing emergence of insulin resistance in children and adolescents,[44] coupled with data from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study that indicates an association between atherosclerosis and factors associated with the prediabetic stage, notably hyperglycemia and adiposity, in young adults,[45] makes the investigation of agents that reduce insulin resistance an urgent priority.

Therapeutic Approaches Targeting Insulin Resistance

While IGT is beginning to be recognized as a clinical entity, current recommendations for management interventions do not extend to the use of pharmacologic agents at this stage in the development of diabetes. However, because of the close association between insulin resistance and a number of CVD risk factors, insulin-resistant subjects with IGT are at increased risk of both type 2 diabetes and CVD. It is important, therefore, to examine the clinical potential of therapeutic interventions that target the underlying disease by addressing insulin resistance and other risk factors for CVD.

The Benefits of Targeting Insulin Resistance

The UKPDS illustrated the inadequacy of sulfonylureas, metformin, and insulin in reducing the macrovascular complications of the syndrome,[46] which account for 80% of diabetes-related morbidity and mortality.[47] Furthermore, it is becoming apparent that macrovascular complications are not solely associated with chronic hyperglycemia, but stem from a complex set of interrelated metabolic abnormalities linked by a common feature—insulin resistance. Importantly, many components of IRS are present in individuals prior to the onset of diabetes and are linked to the progression from IGT to clinical diabetes, and to the development of CVD. Thus, management strategies that target the underlying defects—in particular, insulin resistance and ß cell dysfunction—may be more successful in delaying disease progression than traditional strategies. In fact, results from the Troglitazone in the Prevention of Diabetes (TRIPOD) study support preclinical data highlighting the potential of thiazolidinediones (TZDs) to delay disease progression.[48] This trial was designed to assess the impact of troglitazone therapy in women with a history of gestational diabetes mellitus, which is a risk factor for IGT and type 2 diabetes.[49] Preliminary data indicate a more than 55% decrease in type 2 diabetes incidence in women treated with troglitazone compared with those receiving placebo during 30 months of follow-up.[48]

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In addition to these promising data, there are signs that TZDs, by targeting insulin resistance, beneficially impact many aspects of IRS and thus have the potential to reduce the burden of macrovascular complications in type 2 diabetes. However, it will also be important to evaluate the long-term safety of TZDs when assessing their risk:benefit profile. For example, preliminary clinical trials indicate that these agents induce fluid retention and may increase the risk of developing edema, which develops in approximately 5% of patients during TZD treatment.[50] As fluid retention may exacerbate heart failure, TZDs are not recommended for use in individuals with New York Heart Association (NYHA) Class 3 and 4 cardiac status. TZD therapy is also associated with weight gain, although this is usually moderate and typically plateaus over time. Anemia, reported in a small proportion of patients taking a TZD in clinical studies, is generally mild to moderate in severity and did not usually result in discontinuation of treatment. Although troglitazone was withdrawn due to hepatic dysfunction, this does not appear to be a class effect of the TZDs.[51] The risk:benefit profile of the TZDs can only be confirmed through prospec-

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tive, long-term, controlled clinical trials that assess clinical outcomes. For example, currently underway, the Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM) study is investigating whether the TZDs can delay—or even prevent—progression from prediabetes to type 2 diabetes. The results of ongoing trials will have implications for the future management of patients at risk of developing diabetes, as well as those with established clinical disease. ■

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Main Points

- Evidence points to a continuum of coronary heart disease (CHD) risk that is dependent on glucose levels across the spectrum from normal glucose tolerance through impaired glucose tolerance to diabetes.
- Individuals with type 2 diabetes have a 2- to 4-fold increased risk of developing CHD compared with their counterparts without diabetes.
- Insulin resistance should be regarded, in parallel with hypertension and dyslipidemia, as a therapeutic target that requires intervention.
- Hyperglycemia has emerged as a leading candidate responsible for the excess CHD risk in diabetes.
- Management strategies that target the underlying defects—in particular, insulin resistance and ß cell dysfunction—may be more successful in delaying diabetes progression than traditional strategies.

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