Insulin Resistance: From Benign to Type 2 Diabetes Mellitus

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Type 2 diabetes has become the most frequently encountered metabolic disorder in the world, currently affecting 5% to 10% of most populations, and the incidence continues to grow among developing nations. Two fundamental abnormalities are involved in the pathogenesis of type 2 diabetes: Resistance to the biologic activities of insulin in glucose and lipid metabolism and inadequate insulin secretion from the pancreatic ß cells. In genetically predisposed individuals, type 2 diabetes is pathogenically linked with progressive obesity, especially adiposity that is visceral or ectopic in distribution. While microvascular complications (retinopathy, nephropathy, neuropathy) continue to plague patients with longstanding type 2 diabetes, cardiovascular disease has assumed particular importance, accounting for more than 80% of adverse outcomes among patients. Since the aggressive management of diabetes and its complications poses a considerable challenge, large trials to prevent the progression to overt diabetes in persons at high risk have recently demonstrated that lifestyle modification and pharmaceutical therapy can be successful approaches. A better understanding of the complex relationship between obesity and both the development of type 2 diabetes and its cardiovascular complications may provide additional treatment targets in the future to prevent the devastating chronic morbidity of this disorder.

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Type 2 diabetes is a heterogeneous disorder. The pathogenesis of type 2 diabetes involves 2 fundamental abnormalities: Resistance to the biologic activities of insulin in glucose and lipid metabolism, and inadequate insulin secretion from the pancreatic ß cells.[1] In persons who are genetically predisposed, type 2 diabetes commonly arises with progressive obesity, especially

Table 1
Influences of Obesity on the Pathogenesis of Type 2 Diabetes and Cardiovascular Disease

- Factors secreted from adipose tissue with adverse effects; eg, free fatty acids, cytokines (tumor necrosis factor-α)
  - Promote resistance to insulin effects in skeletal muscle and liver
  - Contribute to endothelial dysfunction
  - Chronic exposure may adversely affect pancreatic ß cell function
- Factors secreted from adipose tissue with salutary effects; eg, adiponectin
  - Enhances insulin sensitivity in skeletal muscle and liver
  - Protective effects on vascular function
  - Unknown effects on pancreatic ß cell
- Factors related to local accumulation of visceral fat and increased tissue acyl CoA derivatives
  - Specific defects in insulin signal transduction
  - Toxic effects on pancreatic ß cell insulin secretion and ß cell mass

visceral or ectopic in distribution.[2] Globally, type 2 diabetes has become the most frequently encountered metabolic disorder, currently affecting 5% to 10% of most populations in the modern world, and the incidence continues to grow among developing nations.[3] Among the many potential chronic complications of type 2 diabetes, cardiovascular disease (CVD) has assumed particular importance and accounts for more than 80% of adverse outcomes among patients. This article will summarize the contribution of insulin resistance and ß cell inadequacy to the pathogenesis of type 2 diabetes, with particular attention to the role of visceral adiposity in the development of diabetes as well as cardiovascular disease.

Insulin Resistance

While diabetes mellitus per se is always diagnosed by predetermined levels of hyperglycemia,[4] it is most important to recognize that the abnormal glucose metabolism in type 2 diabetes develops over a protracted period of time, during which period, individuals are at high risk for CVD.[5] Resistance to the action of insulin arises first, in association with a constellation of metabolic risk factors recognized as the metabolic syndrome. Hyperglycemia occurs later, as pancreatic insulin secretion eventually fails to provide sufficient insulin for the metabolic needs of the body (see below).

Because of differences in tissue sensitivities to insulin action, the development of insulin resistance initially results in decreased disposal of glucose into muscle leading to postprandial hyperglycemia, followed later by a more pronounced deficiency of insulin action, resulting in increased hepatic glucose output and overt fasting and all-day hyperglycemia.[6] Insulin resistance most often arises in genetically predisposed individuals in the setting of sedentary lifestyle and caloric excess. Prospective studies have shown that reduced insulin sensitivity is the first detectable abnormality in patients in whom diabetes is destined to develop, occurring many years before the onset of clinical type 2 diabetes.[7] Alterations in insulin secretion were detectable only 3-5 years before the onset of overt hyperglycemia. Several ethnic minority populations have a higher incidence of insulin resistance and type 2 diabetes compared with Caucasians of European descent, likely due to their propensity to store calories readily in adipose depots that have adverse metabolic effects (see below). This potentiated storage of excess energy intake likely arises from the notion of a metabolically "thrifty" phenotype, which has been likely to confer survival in times of caloric restriction, enriching the ancestral gene pool of these populations.[8] The frequent concomitant inheritance of glucose intolerance and type 2 diabetes in families and identical twins also provides evidence of a strong genetic component.

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Obesity and the Development of Insulin Resistance

The close association between the ongoing worldwide epidemic of obesity, driven by excess caloric intake and sedentary lifestyles, and the development of insulin resistance and type 2 diabetes has highlighted the key role of adiposity in the pathogenesis of these disorders (Table 1). A large body of recent

research has begun to elucidate the underlying pathophysiologic mechanisms linking adipose tissue with insulin sensitivity as well as vascular endothelial dysfunction.[9] One of the most revolutionary concepts is that adipose tissue is not only a simple reservoir for energy stored as triglycerides but also serves as an active secretory organ, releasing many peptides, complement factors, and cytokines into the circulation.[10] The secretion of these factors is altered by increasing overall adiposity as well as the distribution of the stored adipose tissue, in particular attributing adverse effects of obesity to visceral and intra-abdominal adiposity as opposed to subcutaneous adipose tissue which appears to be less pathogenic. A hypothesis has also been developed that attributes the adverse effects of excessive lipid "supply" by a mechanism currently referred to as "lipotoxicity."[11] This effect is analogous to "glucotoxicity" where even mild hyperglycemia adversely affects glucose-coupled insulin secretion and contributes to further dysfunction of the pancreatic insulin-secreting cells.[6]

Normally, insulin-signaling proceeds by insulin binding to its cell surface receptor protein, which activates the intrinsic tyrosine kinase activity of the receptor.[1] The activated receptor kinase then phosphorylates protein substrates within the cell on tyrosine residues. These tyrosine phosphorylated insulin receptor substrate proteins act as "docking" sites, binding other cellular signaling molecules that serve as "adapters" in the formation of complexes of intracellular signaling proteins. Downstream from these signaling complexes, the various cellular actions of insulin on glucose and lipid metabolism as well as cell growth are stimulated.

Recent research has delineated specific mechanisms whereby excess adiposity can influence the normal cellular actions of insulin and contribute to insulin resistance. Among the factors released by adipose tissue, free fatty acids (FFA), which comprise the lipid side-chains of the triglyceride molecule, are elevated in persons with increased visceral adipose tissue.[12] When FFA are elevated for a prolonged amount of time, they have a direct effect on insulin action in skeletal muscle tissue and liver, reducing the normal responses to insulin to promote glucose uptake and to suppress hepatic glucose output, respectively.[12,13] In both of these tissues, FFA increase cellular levels of acyl-CoA derivatives, which leads to an increase in the activity of cellular signaling molecules termed *serine kinases* that oppose the normal tyrosine phosphorylation cascade of the insulin receptor.[14] The increased intracellular lipid accumulation that occurs in obese subjects as "ectopic fat"—that is, triglyceride stored in the target organs themselves rather than in a benign adipose depot—is another important source of intracellular acyl-CoA molecules that can affect normal insulin signal transduction.[9] Other proteins secreted by adipose tissue, including the important inflammatory mediators interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), have adverse effects on energy metabolism and insulin sensitivity in liver and muscle and play key roles in the development of insulin resistance in obesity.

Obesity and Vascular Dysfunction

The cellular mechanisms leading to increased risk of macrovascular disease in obesity and diabetes are currently an area of intensive investigation. Endothelial dysfunction, a deficiency of endothelial nitric oxide production in response to normal secretion signals including insulin and shear stress, is a key abnormality found in insulin-resistant states that leads to hypertension, increased cell-surface adhesion molecules, and other changes that contribute to early processes of atherosclerosis.[15] Vascular dysfunction in insulin-resistant states is believed to result from signaling defects in endothelial and vascular smooth muscle cells due to the effects of circulating mediators, including FFA and cytokines (eg, TNFα). Hyperinsulinemia, resulting from resistance to insulin's metabolic effects, may also play a role in vascular dysfunction by stimulating pathways that continue to respond to the high circulating levels of the hormone.[16] In this setting, the differential maintenance of insulin sensitivity to certain pathways involved in cell proliferation of vascular cells (MAP kinases) in combination with the loss of vascular protective signals (via the phosphatidylinositol 3'-kinase pathway) may contribute to the underlying basis of vascular dysfunction in insulin-resistant states.[17]

As recent work has focused on the identification of specific mechanisms underlying signaling abnormalities in insulin-resistant states,[1] clear similarities have been found between some of the post-receptor defects in insulin action found in its traditional metabolic target tissues and those that are now becoming apparent in vascular cells. In patients with hyperglycemia, additional mechanisms, including excessive oxidative stress due to mitochondrial glucose metabolism and the activation of inhibitory cellular serine kinases and other pathways by glucose metabolites, contributes to endothelial dysfunction.[18] A better understanding of specific pathways of hormone signaling in the vasculature and how they are affected by the increased

circulating levels of insulin and other factors (including FFA and cytokines) will help direct approaches to improving the vascular dysfunction known to be characteristic of the insulin-resistant state.[19]

Adiponectin

Adiponectin is a recently described plasma protein secreted uniquely from adipose tissue that has provided new insight into the interrelationships of obesity, insulin resistance, and CVD.[20] Unlike TNFα and FFA, whose plasma levels are increased in visceral obesity, the levels of adiponectin are reduced in obese subjects.[21]

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Studies of the physiologic role of adiponectin have provided evidence that it enhances insulin action and improves sensitivity as well as having anti-inflammatory protective effects on the vascular endothelium. Adiponectin improves the plasma clearance of FFA, glucose, and triglycerides and suppresses hepatic glucose production.[21] In liver, skeletal muscle, and adipose tissue, the mechanism of action of adiponectin has been shown to involve adenosine monophosphate (AMP)–activated protein kinase (AMP kinase),[22-24] a signaling kinase implicated in the insulin-independent uptake of glucose into skeletal muscle and also in the cellular mechanism of action of metformin. Also, consistent with the influence of visceral adiposity on insulin resistance and the metabolic syndrome, the regulation of circulating levels of adiponectin appears to be at the level of omental adipose tissue as opposed to the subcutaneous depot.[25]

As a link between insulin resistance and endothelial dysfunction, adiponectin also has important salutary effects in vascular tissues. Adiponectin accumulates in the walls of injured vessels[26] and opposes the adverse effects of inflammatory agents such as TNFα, inhibiting TNFα-induced expression of leukocyte adhesion molecules that contribute to the atherogenic process.[27] Vascular reactivity in human subjects has been shown to be closely associated with circulating adiponectin levels.[28,29] Finally, adiponectin can provide protection from the development of atherosclerosis in rodent models.[30-32] Clearly, this important mediator has provided insight into the coordinated pathogenesis of vascular disease in insulin-resistant states with obesity and a new target to potentially reduce risk of vascular disease in type 2 diabetes.

Interestingly, the thiazolidinedione insulin-sensitizing agents have been shown to be a key regulator of adiponectin secretion in both animal models and human subjects with insulin resistance and type 2 diabetes.[25,33] Since these agents are known to dramatically improve insulin action as well as enhance vascular endothelial function, it appears that increasing the circulating levels of adiponectin may be one of the major ways by which the thiazolidinediones can ameliorate many of the pathologic features of the metabolic syndrome.

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Adipose Tissue and ß Cell Function

In persons with obesity and insulin resistance, compensatory increases in insulin secretion from the pancreatic ß cells is a key determinant of glucose homeostasis.[34] Insulin secretion by pancreatic ß cells stimulated by glucose is characterized by 2 phases. The first phase is the rapid release of insulin occurring over minutes and detectable only after the rapid intravenous infusion of glucose. The second phase is a more prolonged release of insulin over hours following food intake or oral administration of glucose. As with other hormones, insulin is released in a pulsatile fashion, and the loss of the first phase of insulin secretion and abnormalities in pulsatility of insulin secretion are early signs of ß cell dysfunction in the development of type 2 diabetes.

In persons with early functional defects in pancreatic insulin secretion, the ß cells are present, but their ability to sense glucose and secrete insulin appropriately is disrupted. The mechanisms underlying these alterations have been shown to involve adverse effects of hyperglycemia and visceral lipid storage in persons with obesity and insulin resistance.[11] The effects of even mild hyperglycemia to cause a deterioration of first phase insulin secretion has been recognized for many years.[35] Since the ß cells maintain their responsiveness for insulin secretion

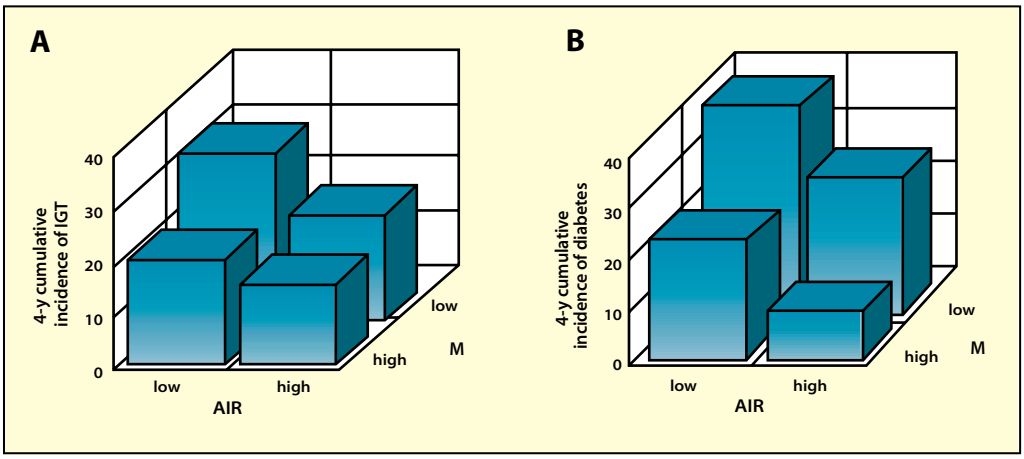

Figure 1. *Contribution of insulin resistance and beta cell dysfunction to the risk of type 2 diabetes.* **(A)** *Progression from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT). Four-year cumulative incidence of IGT in 254 Pima Indians with initial NGT as a function of insulin action (M) and early-phase insulin secretion (AIR) at baseline.* **(B)** *Progression from IGT to type 2 diabetes. Four-year cumulative incidence of type 2 diabetes in 145 Pima Indians with initial IGT as a function of insulin action (M) and early-phase insulin secretion (AIR) at baseline. In both graphs, subjects are divided into those with M and AIR above and below the median. Reproduced with permission from Weyer et al.*[37]

to other secretagogues, this accounts for the regulation of postprandial glucose in many patients following a mixed meal containing proteins as well as the ability of the ß cells to respond to such medications as the sulfonylureas and meglitinides.

More recently, the hypothesis has been developed attributing a deterioration of ß cell function to chronic exposure of high levels of FFA, as occurs in obesity and insulin-resistant states. Analogous to the concept of glucotoxicity, the notion of lipotoxicity has provided insight into potential mechanisms linking the accumulation of visceral adipose tissue with function defects in pancreatic insulin secretion as well as an eventual loss of ß cell mass.[11] According to this hypothesis, under the influence of chronic exposure to long-chain fatty acids in states of deficient leptin action that regulates tissue fat oxidation, these lipid derivatives enter more toxic pathways. This can lead to increased oxidative stress and activation of inflammatory pathways eventually leading to programmed cell death (or lipoapoptosis), especially affecting the pancreatic ß cells. Interestingly, the effect of the thiazolidinedione insulin-sensitizers to protect and improve ß cell insulin content and secretory function appears to be due to an amelioration of this process via a redistribution of adipose tissue and the loss of the adverse effects of the accumulated visceral fat and its secretory products.[36]

Insulin Resistance and ß Cell Function in the Development of Type 2 Diabetes

As noted above, insulin resistance is a principal initiating factor in the development of type 2 diabetes, with a worsening of hyperglycemia closely following the deterioration of ß cell insulin secretion.[34] The progression of glucose tolerance impairment to overt type 2 diabetes in a population at risk closely follows both of these key variables (Figure 1).[37]

Strategies for the Prevention of Type 2 Diabetes

The protracted time course of many years that characterizes the development of type 2 diabetes and hyperglycemia in susceptible individuals provides a clear opportunity for prevention of clinical diabetes.[38] Screening strategies are also warranted because overt type 2 diabetes can often be present with little or no symptoms. This finding was highlighted by the United Kingdom Prospective Diabetes Study (UKPDS) in which it was estimated that at the time diabetes was diagnosed, patients may have had diabetes for the preceding 5-6 years, and many patients already showed signs of diabetes complications.[39] Another major con-

Table 2
Controlled Clinical Trials in the Prevention of Type 2 Diabetes in Populations at High Risk

Clinical Trial	Journal (Year)	Description	Risk Reduction
Da Qing (China)	*Diabetes Care* (1997)	Diet +/- exercise	31-46%
Finnish Prevention Study	*N Engl J Med* (2001)	Intensive lifestyle modification	58%
Diabetes Prevention	*N Engl J Med* (2002)	Intensive lifestyle modification	58%
Program (NIH)		Metformin	31%
STOP-NIDDM	*Lancet* (2002) / *JAMA* (2003)	Acarbose	25%

sideration for the overall prevention of type 2 diabetes is the recognition that cardiovascular risk in patients with diabetes and hyperglycemia is much greater than in those with the metabolic syndrome or impaired glucose tolerance (IGT).[40]

Several large, prospective clinical trials have recently provided insight into preventing overt type 2 diabetes in at-risk populations by modifying lifestyle and using medications (Table 2).[41] Two of these trials studied the effects of lifestyle interventions to delay or prevent the onset of type 2 diabetes in patients with IGT. One study, conducted in Da Qing, China, randomized 577 subjects to a control group or to 1 of 3 active treatment groups: diet only, exercise only, or diet plus exercise. Over the ensuing 6 years, the adjusted proportional hazards analysis revealed that diet, exercise, and diet plus exercise were associated with significant reductions in risk of developing diabetes (31%, 46%, and 42%, respectively).[42] Similar data were obtained in a prospective, randomized study conducted in Finland that also examined the effect of lifestyle modifications on diabetes progression in an IGT population. This study revealed a 58% risk reduction in the progression to diabetes after patients followed an intensive lifestyle modification program.[43] In the Diabetes Prevention Program (DPP) conducted in the United States, a 58% risk reduction was demonstrated in subjects with IGT undergoing intensive lifestyle modification, which consisted of dietary regulation and a weight loss goal of 7% of body weight at entry in the study along with exercise that increases physical activity by 150 min per week, compared with a control group.[38]

While these studies have highlighted the high efficacy of intensive lifestyle modification in the prevention of diabetes, it is also widely appreciated that such lifestyle alterations, especially involving weight loss, are difficult to sustain. Other approaches to the prevention of type 2 diabetes have used pharmacologic interventions. In the DPP, 1 group also received metformin therapy (850 mg twice daily), which significantly reduced the risk of diabetes by 31% compared with placebo but was substantially less effective than the lifestyle intervention.[38] In the European STOP-NIDDM trial, the α-glucosidase inhibitor acarbose, which primarily lowers postprandial glucose excursions, was also shown to be significantly effective in reducing the risk of the incidence of type 2 diabetes in patient with IGT by 25%.[44] Interestingly, the use of acarbose has also been shown to reduce the incidence of cardiovascular risk factors, including hypertension and cardiovascular events, suggesting that the prevention of diabetes and other factors of the metabolic syndrome may help reduce cardiovascular outcomes.

Another influential trial of diabetes prevention in a high-risk group has demonstrated the effects of the insulin-sensitizer troglitazone in women with previous gestational diabetes. While pregnancy is well-recognized to be a state of insulin resistance, gestational diabetes occurs in a small proportion of pregnant women largely because of inadequate pancreatic insulin secretion. The TRIPOD (TRoglitazone In the Prevention Of Diabetes) study conducted by Buchanan and colleagues[45] showed that in a cohort of women with previous gestational diabetes, the onset of diabetes could be reduced by 55%. The protection from diabetes with troglitazone was attributed not

Main Points

- Abnormal glucose metabolism in type 2 diabetes develops over a long time, during which period, persons are at high risk for cardiovascular disease (CVD). Resistance to the action of insulin arises first, in association with the metabolic syndrome. Hyperglycemia occurs later, as the pancreas fails to secrete sufficient insulin for the metabolic needs of the body.
- The thiazolidinedione insulin-sensitizing agents have been shown to be a key regulator of adiponectin secretion in both animal models and human subjects with insulin resistance and type 2 diabetes.[25,33]
- Proteins secreted by adipose tissue, including the important inflammatory mediators interleukin-6 and tumor necrosis factor-α (TNFα), have adverse effects on energy metabolism and insulin sensitivity in liver and muscle and play key roles in the development of insulin resistance in obesity.
- Endothelial dysfunction is a key abnormality found in insulin-resistant states that leads to hypertension, increased cell-surface adhesion molecules, and other changes that contribute to early processes of atherosclerosis.
- Adiponectin has provided new insight into the interrelationships of obesity, insulin resistance, and CVD. Unlike TNFα and free fatty acids, whose plasma levels are increased in visceral obesity, the levels of adiponectin are reduced in obese subjects.

only to its effects as an insulin-sensitizer but was also associated with the improvement in ß cell function that is observed with these agents, as discussed above. In the DPP, a cohort of IGT patients was also treated with troglitazone for a mean of 0.9 years before it was discontinued because of concerns of hepatic toxicity. Preliminary data have shown that troglitazone had a significant effect on reducing the diabetes incidence rate to 3.0/100 person-years, compared with 6.7 and 12.0 in the metformin and placebo participants and similar to the rate of 5.1 in the intensive lifestyle modification group. Interestingly, the effect of troglitazone to prevent diabetes did not persist and was limited to its period of use.[46]

Additional studies are now underway examining the effects of other thiazolidinediones on preventing diabetes in populations having IGT as well as postgestational diabetes. The ß cell secretagogue nateglinide is being tested in an ongoing trial to determine its potential effect in the primary prevention of diabetes.[47] Recent post-hoc analyses have also raised the novel hypothesis that vascular (or unknown) effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril[48] and the HMG CoA reductase inhibitor pravastatin[49] may also protect against the development of type 2 diabetes. These new findings are enticing and emphasize that many potential avenues toward managing the progression of type 2 diabetes as well as its cardiovascular complications warrant further study. ■

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