TYPE 2 DIABETES MELLITUS: Etiology, Pathogenesis, and Natural History

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Type 2 diabetes mellitus is the most common form of diabetes and is currently a major worldwide cause of morbidity and mortality. This is likely to worsen, given the rapidly increasing prevalence of this condition; therefore, an understanding of its etiology and pathogenesis is of considerable importance. By definition, patients with type 2 diabetes have neither autoimmune β cell destruction, as is found in type 1 diabetes, nor one of the other specific causes of diabetes described in Chapter 39. Type 2 diabetes is not a single disease process but instead represents a heterogeneous constellation of disease syndromes, all leading to the final common pathway of hyperglycemia. Many factors, alone or in combination, can cause hyperglycemia; thus, the complexity of the pathogenesis of type 2 diabetes reflects the heterogeneous genetic, pathologic, environmental, and metabolic abnormalities that can exist in different patients.

Normal glucose homeostasis relies on a balance between insulin secretion and tissue sensitivity to insulin. With respect to regulation of glucose metabolism, the tissue effects of insulin on skeletal muscle, liver, and adipose tissue are most important. Three major metabolic abnormalities coexist in type 2 diabetes, each contributing to the hyperglycemic state. These abnormalities are summarized in Fig. 41-1. To begin at the hepatic level, the role of the liver in the pathogenesis of type 2 diabetes is overproduction of glucose. Increased basal hepatic glucose production is characteristic of essentially all type 2 diabetic patients with fasting hyperglycemia. Skeletal muscle is depicted as the prototypic peripheral insulin target tissue, because 70% to 80% of all glucose is taken up by skeletal muscle in the in vivo insulin-stimulated state. Target tissues are insulin resistant in type 2 diabetes mellitus, and such resistance has been well described in many studies across a large variety of population groups. Finally, abnormal islet cell function plays a central role in the development of hyperglycemia; decreased β cell function and increased glucagon secretion are standard concomitants of the diabetic state. Taken together, abnormalities in these organ systems account for the syndrome of type 2 diabetes mellitus. In subsequent sections of this chapter, each of these abnormalities will be considered in further detail.

Although the causal mechanisms may be heterogeneous in different type 2 diabetic patient groups, ultimate expression of the hyperglycemic state involves some combination of impaired insulin secretion, insulin resistance, and increased hepatic glucose production, and the relative magnitude and importance of these three common metabolic abnormalities depend on the specific genetic, pathologic, or environmental factors involved in a particular patient.
10% to 15% for Mexican Americans, and these numbers are type 2 diabetes in the world. Among the Pima Indians, 80% of diabetes mellitus; this is the group with the highest incidence of More than 40% of the Pima Indians in Arizona have type 2 diabetes. On assessment of the other twin, type 2 diabetes. Further evidence for a genetic basis comes from striking differences in the prevalence of type 2 diabetes in various ethnic groups that are not explained by environmental factors. The prevalence of type 2 diabetes in the United States is 2% to 4% for Caucasians, but it is 4% to 6% for African Americans and 10% to 15% for Mexican Americans, and these numbers are increasing as the prevalence of obesity is rising at epidemic rates. More than 40% of the Pima Indians in Arizona have type 2 diabetes mellitus; this is the group with the highest incidence of type 2 diabetes in the world. Among the Pima Indians, 80% of 35- to 44-year-old offspring of two parents with type 2 diabetes mellitus before age 45 years have diabetes, and a positive family history of type 2 diabetes is a substantial risk factor for disease development. Clearly, this genetic predisposition interacts with adverse environmental influences, such as obesity and sedentary lifestyle, which are largely responsible for the sharp uptick in type 2 diabetes mellitus incidence in recent years.

Despite the high concordance rate in twins, “garden variety” type 2 diabetes is obviously not simply the result of a single-gene defect; the inheritance pattern of type 2 diabetes does not conform to any recognizable mendelian pattern, and the incidence of type 2 diabetes in first-degree relatives is below what one would expect. In most patients with type 2 diabetes, the disease appears to be a polygenic disorder, in that disease expression depends on multiple gene loci, all of which may have small to moderate effects. It is also likely that type 2 diabetes is multifactorial, meaning that different combinations of gene polymorphisms may exist among patients. A more detailed discussion of possible susceptibility genes will follow later in this chapter. Type 2 diabetes is referred to as a multifactorial disease, in that the genes interact not only with each other, but also with environmental influences. Individuals therefore may be predisposed to develop type 2 diabetes through their inheritance of a particular combination of genes, but acquired environmental factors are necessary to bring out the phenotypic manifestation of hyperglycemia.

Although multiple genes are involved in the pathogenesis of diabetes in most patients, a small number of patients have a monogenic form of this disease. In these forms of diabetes, environmental factors play little or no role in determining the phenotypic expression. These single-gene mutations may confer a defect in insulin secretion or insulin action, and each will be discussed specifically later in the chapter.

**GENETIC FACTORS**

Abundant evidence supports the view that a strong genetic component contributes to type 2 diabetes. Although many patients have a positive family history for this disease, perhaps the strongest evidence comes from twin studies. In one study, 53 twin pairs were examined, in whom one twin was ascertained to have type 2 diabetes. On assessment of the other twin, type 2 diabetes had developed in 91% (48/53) of the co-twins. Although the five discordant twins were not overtly diabetic, they had mild glucose intolerance and abnormal insulin responses during oral glucose tolerance tests, suggesting that they too might ultimately progress to overt disease.

Further evidence for a genetic basis comes from striking differences in the prevalence of type 2 diabetes in various ethnic groups that are not explained by environmental factors. The prevalence of type 2 diabetes in the United States is 2% to 4% for Caucasians, but it is 4% to 6% for African Americans and 10% to 15% for Mexican Americans, and these numbers are increasing as the prevalence of obesity is rising at epidemic rates. More than 40% of the Pima Indians in Arizona have type 2 diabetes mellitus; this is the group with the highest incidence of type 2 diabetes in the world. Among the Pima Indians, 80% of 35- to 44-year-old offspring of two parents with type 2 diabetes mellitus before age 45 years have diabetes, and a positive family history of type 2 diabetes is a substantial risk factor for disease development. Clearly, this genetic predisposition interacts with adverse environmental influences, such as obesity and sedentary lifestyle, which are largely responsible for the sharp uptick in type 2 diabetes mellitus incidence in recent years.

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**ACQUIRED FACTORS**

**Lifestyle: Diet, Exercise, and Obesity**

Acquired factors play a major role in the development of type 2 diabetes in genetically predisposed individuals; this is clearly demonstrated by assessment of the impact of lifestyle changes on prevalence of diabetes in various ethnic populations. The prevalence of diabetes increases as ethnic groups migrate from lesser developed to more urbanized areas or simply change from an agrarian to a more sedentary, urban lifestyle. The former has been illustrated by surveys in Japanese subjects. In rural Japan, the prevalence of type 2 diabetes was approximately 4%, whereas among Japanese who have immigrated to the United States, the prevalence rises to more than 21%. This is also the case in the Pima Indians, who in Arizona have adopted a largely “Westernized” lifestyle, although those living in northwestern Mexico have remained agrarian. The Indians in Arizona have a prevalence of diabetes of 54% and 37% for men and women, respectively, whereas the Mexican Indians have a prevalence of 6% and 11%, respectively.

It is likely that nutrition and lifestyle are the environmental factors that explain the difference in diabetes prevalence in genetically similar populations. Adoption of an urbanized, Westernized lifestyle is associated with change to a diet that has a higher content of total calories, fats, and refined carbohydrates. For example, the mean daily intake of fat among Japanese men living in Japan was reported to be 16.7 g by contrast, in Japanese American men, the mean intake was 32.4 g. In addition, the level of physical activity is lower among ethnic groups living in the United States compared with the same ethnic groups living in their country of origin. These lifestyle changes obviously predispose to the development of obesity, and overwhelming evidence suggests that obesity is a major factor in the development of diabetes. The role of obesity in the pathogenesis of diabetes will be discussed in detail later in this chapter. Recent evidence supporting the role of lifestyle factors in the development of diabetes has come from the Diabetes Prevention Program. In this study, intensive lifestyle modification, consisting of dietary change and increased exercise, led to a 58% reduction in the progression of impaired glucose tolerance to diabetes over a 2.8 year period.

The extent of the contribution of these lifestyle factors, independent of their association with obesity, to the development of diabetes remains unclear. For example, it is not known whether specific dietary components, such as a diet that is rich in satu-
rated fat or highly refined carbohydrates, play an independent role in the pathogenesis of type 2 diabetes. With regard to exercise, however, evidence from experimental and epidemiologic studies indicates that subjects with lower physical activity levels are more prone to develop diabetes, independent of obesity.  

Low Birth Weight

Low birth weight as a risk factor for the development of insulin resistance and diabetes mellitus later in life has been described in many populations over the past 2 decades.  

The mechanisms responsible for this association are unknown but may be related to epigenetic fetal adaptation to nutritional stimuli or excess fetal glucocorticoid exposure.

Aging

Aging is associated with a decrease in glucose tolerance, which appears to be due to a decline in both insulin sensitivity and insulin secretion. However, age-related factors such as reduced physical activity and increased fat accumulation are at least in part responsible for this phenomenon. Obviously, type 2 diabetes incidence increases with age, but whether the aging process per se is contributory remains unclear.

In summary, in most subjects, type 2 diabetes is a heterogeneous disorder that results from a complex interaction between genetics and environmental influences such as obesity and other acquired factors.

Natural History of Type 2 Diabetes

The pathophysiologic findings depicted in Fig. 41-1 represent a single point in time after overt type 2 diabetes has developed. However, such an analysis does not reveal the progressive evolution of this disease. Fig. 41-2 presents a schematic description of the natural history or progression to type 2 diabetes. Evidence indicates that in most populations, those who evolve to type 2 diabetes begin with insulin resistance. Insulin resistance can be a primary inherited feature, but acquired factors such as obesity, sedentary lifestyle, and aging (particularly obesity) also can be causal or can exacerbate underlying genetic mechanisms of decreased insulin sensitivity. In an attempt to overcome insulin resistance, the β cell increases insulin secretion, resulting in hyperinsulinemia, which is able to maintain relatively normal glucose tolerance. In a subpopulation of subjects, however, this hyperinsulinemic response is insufficient to fully compensate for the prevailing insulin resistance, and impaired glucose tolerance (IGT) develops. Although a percentage of subjects with IGT may revert to normal glucose tolerance, IGT should be considered an intermediate stage in the development of type 2 diabetes, with many subjects eventually progressing to frank expression of the disease.

The proportion of IGT subjects who progress to type 2 diabetes depends on the particular ethnic groups studied and the methods of assessment used. For example, in the National Institutes of Health (NIH)-sponsored multicenter Diabetes Prevention Program, ≈10% of patients with IGT developed type 2 diabetes mellitus per year. During the transition from IGT to frank type 2 diabetes, at least three pathophysiologic changes can be observed. First is a marked fall in β cell function and insulin secretion. Whether this decrease is due to preprogrammed genetic abnormalities in β cell function, to acquired defects (such as glucotoxicity or lipotoxicity), or to both remains to be elucidated. Nevertheless, a marked decrease in β cell function accompanies this transition, and most believe that this decreased β cell function is the major contributor to the progression to type 2 diabetes mellitus. A second metabolic change is seen at the level of the liver. Subjects with IGT have normal basal rates of hepatic glucose output (HGO), whereas patients with fasting hyperglycemia have increased HGO. Thus, the capacity of the liver to overproduce glucose is an important contributory factor (albeit secondary) to the pathogenesis of type 2 diabetes. Finally, many but not all studies have indicated that patients with type 2 diabetes are more insulin resistant than are those with IGT. Most likely, this increase in insulin resistance is secondary to gluco-toxicity or to other acquired factors.

Evidence implicating insulin resistance as a primary defect comes principally from studies examining subjects who are at increased risk for developing diabetes. One such group consists of individuals whose parents have type 2 diabetes. Using intravenous glucose tolerance tests (GTTs), Warram and coworkers evaluated 155 nondiabetic offspring whose parents both had type 2 diabetes. During a follow-up period averaging 13 years, type 2 diabetes developed in 16% of the total group. However, when offspring were categorized on the basis of insulin sensitivity at initial testing, the cumulative incidence of diabetes was 60% among subjects with preexisting insulin resistance and less than 5% in insulin-sensitive offspring. Thus, insulin resistance and hyperinsulinemia (rather than hypoinsulinemia) characterized the prediabetic state, and this occurred irrespective of obesity and antedated by many years the subsequent development of impaired insulin secretion and overt type 2 diabetes.

Studies in ethnic populations with a high prevalence of type 2 diabetes also have provided data supporting a primary role for insulin resistance in diabetes development. Thus, among Pima Indians, hyperinsulinemia and an associated decrease in insulin-mediated glucose disposal are early abnormalities that predict the subsequent development of both IGT and type 2 diabetes. Pima Indians with IGT who progress to type 2 diabetes have lower insulin levels 2 hours after a glucose load than do those who continue to have IGT or who return to normal glucose tolerance. Similar results come from studies of Micronesians in Nauru, a population with a prevalence of type 2 diabetes of approximately 30%. Again, in this population, IGT and type 2 diabetes were most likely to develop in those with hyperinsu-
linemia at baseline, but progression from IGT to type 2 diabetes could be predicted by lower baseline insulin responsiveness to a glucose challenge.

Further evidence comes from studies in first-degree relatives of type 2 diabetic patients. In these studies, peripheral insulin resistance and hyperinsulinemia were found in normoglycemic relatives of diabetic patients. First-degree relatives with IGT displayed insulin resistance but also exhibited defects in insulin secretion that were not apparent in those with normal glucose tolerance.

In summary, the phenotypic manifestation of type 2 diabetes mellitus involves elevated HGO, impaired insulin secretion, and peripheral insulin resistance. Type 2 diabetes mellitus has a strong genetic component, and studies of prediabetic subjects indicate that in most populations, insulin resistance, accompanied by hyperinsulinemia, exists before any deterioration in glucose homeostasis occurs. After a period of compensatory hyperinsulinemia with normal glucose tolerance, β cell insulin secretion declines, and IGT and eventually overt type 2 diabetes mellitus result.

In the remainder of this chapter, abnormalities of insulin secretion, insulin action, and hepatic glucose metabolism in type 2 diabetes are reviewed, with particular attention to basic mechanisms (where known) and their applicability to etiology.

Pathophysiology of Type 2 Diabetes Mellitus

**ABNORMAL PANCREATIC β CELL FUNCTION**

Obesity is a major cause of insulin resistance, and as was described earlier, the β cell compensates for decreased insulin sensitivity by increasing insulin secretion. In normal glucose-tolerant subjects, the increase in insulin secretion that occurs with insulin resistance is described by a hyperbolic relationship (Fig. 41-3). Although this quantitative increase in insulin secretion in response to decreased insulin sensitivity should be viewed as an appropriate response, subtle qualitative changes in insulin secretion also are noted in the insulin-resistant state. Insulin normally is secreted in rapid regular pulses with a 5 to 15 minute frequency superimposed on slower ultradian oscillations every 80 to 150 minutes. These normal rapid, regular pulses are replaced by disordered pulses in obese subjects with insulin resistance and also in the insulin-resistant but glucose-tolerant offspring of subjects with type 2 diabetes. Indeed, insulin secretory pulse frequency has been shown to correlate inversely with peripheral insulin sensitivity.

**Insulin Secretion in Subjects With Impaired Glucose Tolerance**

In subjects with IGT, both quantitative and qualitative defects in insulin secretion are usually present, although this can be variable. Part of this variability may be explained by the heterogeneity of this condition, as some subjects with IGT will revert to normal glucose tolerance, a proportion will progress to frank type 2 diabetes, and others will continue to have IGT for many years.

With regard to the hyperbolic relationship between β cell function and insulin sensitivity, subjects with IGT secrete less insulin than is appropriate for their degree of insulin resistance. Furthermore, using the graded glucose infusion method, Polonsky has shown that subjects with IGT secrete less insulin at any given glucose level than do normoglycemic subjects matched for a similar degree of insulin resistance and obesity (Fig. 41-3). Insulin-resistant subjects with IGT who have progressive impairment in insulin secretion are most likely to develop full-blown type 2 diabetes.

Insulin secretion in response to a sustained intravenous glucose stimulus is normally biphasic: A rapid rise in insulin levels within 1 to 3 minutes (first phase) is followed by a return to baseline within 6 to 10 minutes with a subsequent gradual increase (second phase). Subjects with IGT have a reduction in both first- and second-phase responses to glucose, and a further qualitative defect in insulin secretion in IGT is the replacement of rapid regular secretory oscillations with disorganized pulses.
Insulin Secretion in Subjects With Type 2 Diabetes

The abnormalities of insulin secretion described in subjects with IGT are also present in type 2 diabetes, although to a more marked degree. β cell function progressively deteriorates during the natural history of type 2 diabetes. This decline in β cell function is evident not only during the conversion from compensated insulin resistance to IGT and subsequently to overt type 2 diabetes, but also during the progressive course of established type 2 diabetes after its initial onset.50

Basal insulin levels usually are normal or increased in type 2 diabetes. Indeed, obese subjects with type 2 diabetes can have basal insulin levels severalfold higher than normal, but this does not mean that basal β cell secretory function is normal, because the prevailing plasma glucose level also must be taken into account.51-53 Hyperglycemia is the major stimulus for insulin secretion, and when normal individuals are made hyperglycemic by infusion of glucose, circulating insulin levels are much higher than those found in type 2 diabetes.51,52 Thus, patients with type 2 diabetes maintain normal or increased basal insulin levels only in the face of the enhanced stimulus of fasting hyperglycemia, which indicates an underlying impairment in the sensitivity of the β cell to glucose. Stimulated insulin levels in type 2 diabetes can be low, normal, or high depending on factors such as the severity of diabetes, the degree of obesity, and the preceding level of diabetic control.13,14,44

In Response to Intravenous Glucose

In type 2 diabetes, defects in the insulin secretory response to intravenous glucose are observed consistently. Once fasting plasma glucose levels exceed 126 mg/dL, the first-phase insulin response to intravenous glucose characteristically is completely absent. This relationship is shown in Fig. 41-5.1,54,55

It is interesting to note that acute or first-phase insulin secretion in response to nonglucose stimuli such as arginine or isoproterenol is relatively preserved; this finding indicates a functionally selective β cell defect in response to glucose stimuli in type 2 diabetes. Because the acute insulin response to intravenously administered arginine or isoproterenol increases as the glucose concentration is raised, Porte and colleagues have attempted to quantitate this effect of glucose by plotting the increase in acute insulin response to arginine or isoproterenol pulses as a function of increasing plasma glucose level.1,14,55 The slope of this relationship is termed the glucose potentiation slope, and by this analysis, glucose potentiation of β cell function is also reduced in type 2 diabetes.1,14

Although absent first-phase insulin secretion may be a marker for β cell dysfunction, it is unlikely to be an important cause of glucose intolerance or hyperglycemia. Thus, mildly hyperglycemic and severely hyperglycemic type 2 diabetic patients are equally deficient in first-phase insulin secretion, implying that this deficiency does not play a role in further deterioration in glucose tolerance from mild to severe fasting hyperglycemia. Furthermore, in selected patients with normal glucose tolerance in whom type 1 diabetes eventually develops, the acute insulin response to intravenous glucose is absent during the normal stage and therefore does not cause hyperglycemia.57 Finally, α-adrenergic blockers can substantially restore the acute insulin response to intravenous glucose without major improvement in fasting glycemia or glucose tolerance.

Second-phase insulin secretion, which is assessed with the hyperglycemic clamp or the graded intravenous glucose infusion technique (see Fig. 41-4 for details), is markedly reduced in individuals with type 2 diabetes compared with normal subjects and those with IGT. In general, the more severe the diabetes, the lower is the second-phase insulin response.1,56

In Response to Oral Glucose and Mixed Meals

The insulin response in type 2 diabetes to oral ingestion of glucose or mixed meals is far more variable than the response to intravenous glucose. After oral glucose, insulin levels are usually subnormal in type 2 diabetes,13,36 although this might not always be the case in patients with mild hyperglycemia.44 This heterogeneity is depicted in Fig. 41-6, which summarizes the results of oral GTTs in a wide spectrum of normal and type 2 diabetic subjects.56 As can be seen, hyperinsulinemia frequently exists in mild states of glucose intolerance. In individuals with mild diabetes, insulin levels generally are in the “normal range,” although inappropriately or relatively low for the degree of hyperglycemia and insulin sensitivity. With

![FIGURE 41-5. First-phase insulin release in response to the intravenous administration of glucose in normal and type 2 diabetic (non-insulin-dependent diabetes [NIDD]) subjects. Mean fasting plasma glucose concentrations were 83 ± 3 mg/dL in normal subjects and 160 ± 10 mg/dL in type 2 diabetic subjects. (Data from the American Diabetes Association, Inc., from Ward WWK, Beard JC, Halter JB, et al: Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus, Diabetes Care 7:491–502, 1984.)](image-url)
more severe diabetes, absolute stimulated insulin levels are uniformly low.

In type 2 diabetes, the defect in β cell function is relatively (but not completely) specific for glucose stimuli. The relative preservation of insulin responses to nonglucose stimuli, such as certain amino acids and the incretin gut peptides, means that type 2 diabetic patients have a better insulin response to mixed meals than to oral glucose. Thus, in mild type 2 diabetes, insulin responses to mixed meals may be delayed, but postprandial hyperglycemia, coupled with other insulinogenic factors, often leads to exaggerated insulin responses 2 to 4 hours after meal ingestion. However, with more severe hyperglycemia, decreased insulin levels are more common. Because oral GTTs represent a rather nonphysiologic stress by which to assess β cell function, it is important to keep in mind that in the free-living state, when patients are consuming mixed meals, absolute insulin levels can be relatively preserved in type 2 diabetes.

**Proinsulin Secretion**

Another factor related to hyperinsulinemia in type 2 diabetes is circulating proinsulin levels. Proinsulin is secreted by β cells concomitantly with insulin and cross-reacts with insulin in most insulin immunoassays, thus contributing to the total measured immunoreactive insulin level. In normal subjects, proinsulin represents only a small portion (3% to 7%) of the insulin-like material secreted by β cells. However, using proinsulin-specific immunoassays, several groups have shown that in hyperinsulinemic states and in many cases of type 2 diabetes, an increased proportion of proinsulin is released and contributes to the measured insulin in standard immunoassays, so true insulin levels are overestimated. When corrected for this factor, basal insulin levels may be normal or moderately elevated in type 2 diabetes.

**Mechanisms of β Cell Dysfunction**

The precise cellular mechanisms underlying β cell dysfunction in type 2 diabetes are unclear, but they most likely represent a combination of genetic and acquired factors.

The overall mass of β cells changes in obesity and type 2 diabetes. β cell mass reflects the balance between new islet formation (neogenesis) and β cell loss due to apoptosis. Longitudinal studies in animal models suggest that β cell mass increases appropriately in response to a decrease in insulin sensitivity and cross-sectional data from humans have long revealed an expanded β cell mass in obesity. In contrast, β cell mass is reduced in type 2 diabetes. On the basis of murine models and cross-sectional autopsy data from humans, diminished β cell mass is thought to be due to accelerated β cell apoptosis and the failure of islet neogenesis and β cell replication to compensate for this loss.

It has been theorized that lipid accumulation in the β cell is implicated in the apoptotic process and the development of impaired insulin secretion in type 2 diabetes. This is referred to as lipotoxicity and may involve excess fatty acids entering β cells, thus triggering the apoptotic cellular response.

A body of evidence also suggests a role for islet amyloid polypeptide (IAPP) in the loss of β cells. IAPP is synthesized in the β cell and is co-secreted with insulin. IAPP aggregates to form fibrils of amyloid, and islet amyloid is found at autopsy in up to 90% of subjects with type 2 diabetes. In vitro, IAPP is toxic, causing β cell apoptosis, and it may contribute to the reduced β cell mass that is associated with type 2 diabetes.

Insulin secretory abnormalities found in type 2 diabetes are often improved after a period of good blood glucose control, irrespective of the treatment used (diet, insulin, or oral hypoglycemic agents). This partial reversibility is consistent with the idea that, to some extent, the abnormalities may be secondary to hyperglycemia or some other factor associated with uncontrolled diabetes. Support for the “glucotoxicity” theory comes from a variety of in vivo and in vitro studies showing that chronic exposure of islets to hyperglycemia can result in a number of different defects in glucose-induced insulin secretion. It is important to note that when isolated human islets are incubated under euglycemic and hyperglycemic conditions, islets that are exposed to hyperglycemia demonstrate a marked defect in their ability to secrete insulin in response to subsequent glucose stimuli. Although the precise mechanism is unknown, it seems likely that glucotoxicity coupled with lipotoxicity plays some role in the impaired β cell function of type 2 diabetes.

An interesting finding from studies of mouse genetics is that insulin receptor signaling in β cells is important for normal function. Thus, mice in which the insulin receptor gene has been specifically deleted from β cells show a complete loss of first-phase insulin secretion in response to glucose but not arginine, reminiscent of the β cell defect in type 2 diabetes. Second-phase glucose-induced insulin secretion is also blunted in these mice, and they show an age-dependent progressive impairment in glucose tolerance. Glucose-stimulated insulin secretion involves transport of glucose into cells by a specific
glucose transporter, termed GLUT2. Following uptake, glucose is phosphorylated by glucokinase, and subsequent intracellular metabolism of glucose-6-phosphate leads to stimulation of insulin secretion. In mouse studies, genetic deletion of GLUT2 leads to loss of glucose but not arginine-stimulated insulin secretion. It is interesting to note that feeding mice high-fat diets to induce obesity also leads to a decrease in β cell GLUT2 expression, suggesting another mechanism of interaction between acquired environmental factors and β cell dysfunction.

The decrease in β cell mass in type 2 diabetes is in the range of 30% to 50%. However, because sufficient insulin secretory reserve normally exists to sustain an 80% to 90% loss of β cells without the development of hyperglycemia, it follows that decreased functional capacity of the remaining β cells must exist in type 2 diabetes. Indeed, it has been shown that the maximal insulin secretory capacity may be reduced by as much as 80% in type 2 diabetic subjects.52 It is possible that the decrease in β cell mass in type 2 diabetes is somehow causally related to the decreased function of the remaining β cells. Thus, partially pancreatectomized rats and streptozotocin-treated rats display similar insulin secretory defects,51 which suggests that decreased glucose-stimulated insulin secretion with relative preservation of responsiveness to nonglucose stimuli may be a general type of abnormality that may occur in response to a variety of β cell insults.

PERIPHERAL INSULIN RESISTANCE

In addition to impaired β cell function, another primary pathophysiologic disorder underlying type 2 diabetes mellitus is insulin resistance. Insulin resistance is a metabolic state in which a normal concentration of insulin produces a less than normal biological response. This decreased response to insulin can involve any of the multiple metabolic effects of insulin, but from the standpoint of relevance to type 2 diabetes, resistance to the effects of insulin on glucose metabolism has been the most extensively studied. Because insulin travels from the β cell through the circulation to the target tissue, events at any of these loci can influence the ultimate action of the hormone.

Causes of Peripheral Insulin Resistance

Circulating Factors That Influence Insulin Action

Hormonal antagonists include all known counterregulatory hormones such as cortisol, growth hormone, glucagon, and catecholamines. In well-known syndromes (e.g., Cushing’s disease, acromegaly), elevated levels of these hormones can induce an insulin-resistant diabetic state. However, in the usual case of obesity or type 2 diabetes, excessive levels of these counterregulatory hormones are not an important contributory factor to insulin resistance.

As the body’s largest endocrine organ, adipocytes secrete a number of polypeptides, called adipokines, into the circulation. In turn, these adipokines (i.e., adiponectin, leptin, resistin, retinal binding protein 4, and others) exert distal effects on glucose homeostasis in an endocrine fashion. The effects of adipokines will be discussed later in the chapter.

Several years ago, Randle and coworkers hypothesized that the elevated circulating levels of free fatty acids (FFAs) found in obesity and type 2 diabetes impair peripheral glucose utilization.74 Substantial evidence indicates that FFAs do indeed contribute to insulin resistance, although the mechanisms differ from those originally proposed by Randle. FFAs also play an important role in the regulation of HGO and contribute to hepatic insulin insensitivity in obesity and type 2 diabetes. These mechanisms will be discussed in greater detail later in this chapter.

Other circulating antagonists, such as antibodies against the insulin molecule or against the insulin receptor, are rare causes of insulin resistance and are discussed later in the chapter under “ Syndromes of Severe Insulin Resistance.”

Impaired Access of Insulin to Target Cells

Because insulin must travel from the circulation to target tissues to elicit biological effects, any defect in this transfer could lead to functional insulin resistance. Compared with secretion into the circulation, the passage of insulin from the plasma compartment to tissue sites of action is markedly delayed, and in vivo effects of insulin in stimulating glucose disposal are well correlated with the appearance of insulin in the interstitial fluid.75 Lymph and interstitial insulin levels are ≈40% lower than those in plasma,75,76 which indicates that peripheral tissues are more sensitive to insulin than was previously recognized. Furthermore, the possibility arises that either the rate or the amount of insulin being transferred from the plasma to the interstitial compartment could be abnormal in type 2 diabetes or obesity, thereby contributing to the insulin-resistant state.77,78 Recent studies indicate that transport of insulin across the capillary in vivo occurs by diffusion76 and is not receptor mediated, as was previously suggested.79 Transport by diffusion fits with the finding that transcapillary passage is comparable in normal subjects, insulin-resistant nondiabetic subjects,80 and those with type 2 diabetes.81 Further evidence that the delayed activation of muscle glucose uptake in obesity and type 2 diabetes is not due to impaired transcapillary transport of insulin comes from a study by Nolan and coworkers.76 This study showed that the kinetic defect in the ability of insulin to stimulate leg glucose uptake was not accompanied by any delay in the activation of leg muscle insulin receptors by insulin, thus implying that the kinetic defect is distal to the insulin receptor.

Another physical factor that may relate to insulin resistance is muscle capillary density, which correlates with in vivo insulin sensitivity.82 Laakso and coworkers have shown that insulin, at least at pharmacologic levels, increases leg blood flow.83 Because tissue glucose uptake is a product of blood flow and the arteriovenous glucose difference, increased leg blood flow could contribute to overall glucose disposal. Similar studies performed in obese subjects and in subjects with type 2 diabetes revealed a decrease in the insulin-induced increase in leg blood flow, which may explain part of the decrease in total leg glucose uptake.85 However, others found no effect of insulin on blood flow,86 and Utriainen and colleagues used 13O [H2O] and positron emission tomography to confirm enhancement of leg muscle blood flow by pharmacologic insulin levels, but no difference in the response between type 2 diabetic and normal control subjects.85

Although some of these factors might be contributory, they cannot explain the major component of insulin resistance in type 2 diabetes and obesity, because numerous studies have demonstrated profound in vitro insulin resistance in tissues and cells from these patients.

Cellular Defects in Insulin Action

Available evidence points to a target tissue defect as the major cause of insulin resistance in type 2 diabetes. Before potential causes are considered, it is useful to review some general concepts concerning normal insulin action (Fig. 41-7). Insulin first binds to its cell surface receptor, a heterotetrameric glycoprotein
The effects of insulin are distinct from those leading to activation of glucose transport. Even a single action of insulin such as stimulation of glucose transport can involve more than one signaling pathway. Several cytosolic protein substrates of the insulin receptor are phosphorylated on tyrosine residues within seconds of insulin binding to its receptor. The first of these substrates to be identified was insulin receptor substrate 1 (IRS-1). 

IRS-1 belongs to a growing family of proteins that includes IRS-2, IRS-3, IRS-4, and a protein termed shc, which are immediate substrates of the insulin receptor kinase involved in insulin signaling. These proteins have no enzymatic activity but act as docking proteins. Tyrosine phosphorylation of these substrates enhances their association with proteins that contain src homology-2 (SH2) domains. These SH2 domains contain \( \approx 100 \) amino acids and can bind to specific short motifs that encompass a phosphotyrosine. The binding of specific SH2 domain–containing proteins to tyrosine-phosphorylated IRS proteins or shc generates multicomponent signaling complexes, which, in turn, modulate the activities of phosphoinositide-3-kinase (PI3K), several serine kinases, and phosphatases that act on key insulin-regulated enzymes and transcription factors.

One of the most important effects of insulin with respect to type 2 diabetes is stimulation of glucose uptake into skeletal muscle, adipocytes, and heart muscle. Under most physiologic circumstances, glucose transport in these tissues is rate limiting for overall glucose disposal. Tissue glucose uptake is mediated by a family of at least five facilitative glucose transporters, each derived from a separate gene. These transporters show a high degree of homology, but each has tissue-specific distribu-
Impaired Glucose Tolerance or Type 2 Diabetes

The frequency of insulin resistance increases as the degree of carbohydrate intolerance worsens. Thus, many, but not all, subjects with IGT are insulin resistant, whereas essentially every type 2 diabetic patient with fasting hyperglycemia displays this abnormality. Numerous studies indicate that insulin resistance is more marked in type 2 diabetes than in the prediabetic IGT state. However, other reports show only a modest increase in the degree of insulin resistance going from IGT to type 2 diabetes. Because most type 2 diabetic patients are overweight, obesity-induced insulin resistance is clearly a major contributing factor in these patients. However, obesity is not the only cause, in that the insulin resistance in obese type 2 diabetic patients exceeds that caused by obesity alone, and nonobese type 2 diabetic patients are also insulin resistant.

All methods of assessing insulin resistance in vivo rely on measurement of the ability of a fixed dose or concentration of insulin to promote glucose disposal. Thus, a blunted decline in plasma glucose concentration after administration of intravenous insulin has been demonstrated in type 2 diabetes. Another approach has been to infuse insulin and glucose at fixed rates while endogenous insulin secretion is inhibited by a combination of epinephrine and propranolol or by somatostatin. With this method, the resulting steady-state plasma glucose level reflects the action of concomitantly infused insulin; the higher the steady-state plasma glucose, the greater is the degree of insulin resistance. Bergman and colleagues’ minimal model is yet another method of assessing in vivo insulin resistance. This method entails computer modeling of plasma glucose and insulin levels after an intravenous glucose bolus to generate an index of insulin sensitivity. With all these methods, type 2 diabetic subjects exhibit a significant decrease in insulin sensitivity compared with controls.

More detailed studies of in vivo insulin resistance have been carried out with the euglycemic glucose clamp method. With this approach, insulin is infused at a constant rate, resulting in a given steady-state plasma insulin level, while plasma glucose is kept constant at a predetermined level by a feedback-controlled variable infusion of glucose. The insulin normally lowers the plasma glucose level by suppressing HGO and by stimulating tissue glucose uptake. During the insulin infusion, the amount of glucose that has to be infused to keep plasma glucose levels constant increases gradually until a steady state is reached. Under these steady-state conditions, the glucose disposal rate provides an excellent quantitative assessment of the biological effect of a particular steady-state insulin level. If a radioactive or stable isotope of glucose is also infused during the study, HGO during the clamp can be quantified. In type 2 diabetes, glucose disposal rates are 30% to 60% lower than those in normal subjects at any given insulin infusion rate. If several studies at different insulin levels are performed in a given subject, dose response curves for insulin-stimulated glucose disposal and suppression of HGO can be constructed. Patients with type 2 diabetes (obese and nonobese) exhibit both a rightward shift in their dose response curve (diminished sensitivity) and a marked decrease in their maximal rate of glucose disposal (decreased responsiveness) (Fig. 41-8). These changes tend to be more pronounced in obese diabetic patients, particularly at maximal glucose disposal rates (see Fig. 41-8). The insulin resistance of obese type 2 diabetic patients is significantly greater than that of nondiabetic obese subjects. Subjects with IGT tend to have a rightward shift in their dose response curves with normal maximal glucose disposal rates (see Fig. 41-8).

Because skeletal muscle is responsible for the great majority of in vivo insulin-stimulated glucose uptake, this tissue must be the major site for resistance to insulin-stimulated glucose disposal. This conclusion is evidenced by the demonstration of insulin resistance in type 2 diabetic patients during forearm perfusion studies. Leg catheterization studies have shown that skeletal muscle accounts for ≈80% of whole-body insulin-mediated glucose uptake, and that leg skeletal muscle is markedly resistant to the ability of insulin to stimulate glucose uptake in type 2 diabetes. Thus, although other insulin target tissues display decreased insulin sensitivity, they do not account for a significant proportion of overall glucose uptake, and one can conclude that all measures of in vivo insulin action on glucose disposal largely assess the resistance of skeletal muscle to take up glucose under the influence of insulin.

PATHOPHYSIOLOGIC ABNORMALITIES IN INSULIN TARGET TISSUES

Skeletal Muscle

The major manifestation of skeletal muscle insulin resistance is decreased glucose disposal. Clearly, insulin action in skeletal muscle involves a cascade of events, and abnormalities anywhere along this sequence can lead to insulin resistance. These defects...
can involve abnormal coupling between insulin receptor complexes and the glucose transport system, decreased activity of the glucose transport system per se, or a variety of intracellular enzymatic defects located in various pathways of glucose metabolism.

**Mechanisms of Skeletal Muscle Insulin Resistance**

As the first step in insulin action, it is apparent that a decrease in cellular insulin receptors could lead to insulin resistance. However, this potential relationship is not as clear as it would seem because a maximal insulin effect is achieved at insulin concentrations that occupy a fraction of the surface receptors, giving rise to the concept of “spare” receptors. A maximal response of glucose transport in adipocytes and muscle is achieved with only 10% to 20% of the receptors occupied.112,113 Once the critical number of receptors needed to generate a maximal response is activated, additional increases in the prevailing insulin concentration lead to increases in receptor occupancy with no further increase in biological response, because a step (or steps) distal to the receptor is now rate limiting. The functional significance is that a decreased number of insulin receptors leads to a rightward shift in the insulin biological function dose response curve, with decreased responses at all submaximal insulin concentrations but a normal maximal response. A reduction in the maximal insulin response generally denotes the presence of a postbinding abnormality. In this context, the term postbinding defect includes abnormalities of insulin receptor function that affect its transmembrane signaling function, such as its kinase activity. A postreceptor defect refers to any abnormality in a step distal to the insulin receptor.

Early studies showed decreased insulin binding to circulating monocytes from obese and IGT subjects and from both obese and nonobese type 2 diabetic patients.114,115 This decreased binding was due to a decrease in insulin receptor number with no change in affinity. Similar results were subsequently obtained, when isolated adipocytes, hepatocytes, and skeletal muscle from obese subjects and patients with type 2 diabetes were used.116,117 The decrease in cellular insulin receptors in obesity and type 2 diabetes may well be secondary to hyperinsulinemia, inasmuch as elevated circulating insulin levels can downregulate receptor number.

A reduction in insulin receptor tyrosine kinase activity in type 2 diabetes generally has been found in patients with normal kinase activity in IGT.78,91,117 The receptor autophosphorylation/kinase defect appears to be generalized to all insulin target tissues and relatively specific for the hyperglycemic insulin-resistant state that is seen in type 2 diabetes.

Emerging evidence points to a role for IRS proteins in the development of insulin resistance. A defect in insulin-stimulated IRS-1 tyrosine phosphorylation is found in skeletal muscle from type 2 diabetic patients, although overall IRS-1 expression is unchanged.118 Serine/thr phosphorylation of IRS proteins is closely associated with reduction of signaling through IRS. Two potential mechanisms may underlie this phenomenon. First, serine phosphorylation may block the interaction of IRS-1 with its target proteins.119 Second, proteosomal-mediated degradation of IRS-1 may be increased.120 Several intermediary lipid metabolites and cytokines have been shown to activate a variety of serine/threonine kinases that induce serine phosphorylation of IRS-1. Serine kinases implicated include c-Jun NH2-terminal kinase (JNK),121 1κB kinase (IKK),122 PKC theta, S6K, and MTOR. It is interesting to note that this places IRS-1 at the intersection of a variety of intracellular pathways, including inflammation, endoplasmic reticulum (ER) stress, and nutrient sensing, all of which can activate serine/threonine kinases that may phosphorylate IRS-1.

IRS-2 is also important for insulin signaling and glucose homeostasis. In mice with disruption of the IRS-2 gene, profound defects in both insulin action (predominantly in the liver) and β cell function develop, progressing to diabetes.123 PI3K plays a key role in mediating the effects of insulin on glucose metabolism.124 Insulin-stimulated PI3K activity in skeletal muscle is reduced in both obese nondiabetic subjects125 and patients with type 2 diabetes.126 This reduction in PI3K activity correlates with the decrease in whole-body glucose disposal.118 An interesting twist on this relates to the regulatory subunits of PI3K. PI3K consists of a catalytic, 110 kDa subunit, as well as a family of regulatory subunits (p50, p55, and p85). If expression of the regulatory and catalytic subunits is unbalanced, with excess levels of the regulatory subunits, then monomeric p50/p55/p85 can bind through their SH2 domains to tyrosine phosphorylated substrates, such as IRS-1. When this happens, they can compete out binding of the dimeric p110.p85 PI3K complex, thus inhibiting PI3K signaling. Activated PI3K stimulates pyruvate dehydrogenase kinase (PDK1) in the plasma membrane, which then leads to activation of AKT and PKC ζ/λ. Both of these latter enzymes are upstream of GLUT4 translocation and are important regulators of glucose transport stimulation. Decreased insulin-induced AKT and PKC ζ/λ activation are widely described in insulin-resistant skeletal muscle from a variety of states.

Insulin-stimulated glucose transport in isolated muscle fibers and adipocytes from type 2 diabetic patients is markedly reduced at all insulin concentrations.127,128 What is the mechanism of this decrease? In adipocytes from type 2 diabetic subjects, decreased GLUT4 levels have been reported. In contrast, skeletal muscle GLUT4 mRNA and protein levels are normal in type 2 diabetics.127,128 Because the muscle of type 2 diabetic patients is not deficient in GLUT4 protein, it appears that the defect in insulin-stimulated glucose transport reflects a decrease in the ability of insulin to signal translocation of GLUT4 to the cell surface.

Indeed, clear evidence suggests that this is the case. For example, Kelley and coworkers used quantitative confocal laser scanning microscopy to examine insulin-stimulated recruitment of GLUT4 to the sarcolemma in muscle biopsies from patients with type 2 diabetes.98 In the basal state, sarcolemmal GLUT4 labeling was similar in diabetic and normal subjects, but in response to insulin, the increase in GLUT4 in type 2 diabetic subjects was only 25% of that in control subjects. A quantitatively similar defect in GLUT4 translocation was found in obese nondiabetic subjects. In both type 2 diabetic subjects and obese nondiabetic subjects, the defect in GLUT4 translocation was associated with marked impairment in insulin-stimulated muscle glucose transport as determined by positron emission tomography. Others using biochemical muscle subfractionation techniques have found a defect in GLUT4 translocation in patients with type 2 diabetes.99

Trafficking of GLUT4 involves a complex system analogous to synaptic vesicle movement, and an expanding list of proteins involved in the regulation of GLUT4 trafficking are being identified.130 Clearly, impaired GLUT4 translocation could be due to a defect in one or more of these GLUT4 vesicle-trafficking proteins, which is an area requiring intensive investigation.

**Oxidative and Nonoxidative Glucose Metabolism in Skeletal Muscle**

By performing indirect calorimetry during glucose clamp studies, one can determine the intracellular fate of glucose by measuring
the percentage of glucose that is oxidized versus that which undergoes nonoxidative glucose metabolism (consisting of storage as glycogen plus glycolysis). The insulin concentrations necessary for half-maximal stimulation of glucose oxidation (=50 mU/L in normal subjects) are lower than those required for stimulation of glucose uptake and storage as glycogen (=100 mU/L). Thus, at low physiologic insulin levels, oxidative glucose disposal is quantitatively more important, but at higher insulin levels, nonoxidative glucose metabolism predominates. Defects in both oxidative and nonoxidative glucose metabolism exist in type 2 diabetes, although the decrease in nonoxidative metabolism is greater. Shulman and coworkers, using nuclear magnetic resonance (NMR) spectroscopy of the gastrocnemius muscle during an infusion of 13C-enriched glucose, showed that during a hyperinsulinemic hyperglycemic clamp study, nonoxidative glucose disposal is highly correlated with rates of skeletal muscle glycogen deposition. Moreover, a 50% reduction in the rate of muscle glycogen synthesis in type 2 diabetic patients was found, and defects in nonoxidative glucose metabolism and muscle glycogen synthesis correlated well with the decrease in whole-body glucose uptake. The reduced muscle glycogen synthesis rate in type 2 diabetes could be the result of a decrease in glucose transport, impaired glucose phosphorylation, or an abnormality in the glycogen synthetic pathway, and decreases in GLUT4 translocation, hexokinase II, and glycogen synthase have been reported. To identify the primary site of the intracellular block in glycogen synthesis, Rothman and coworkers used 31P-NMR during glucose clamp studies to measure glucose-6-phosphate concentrations in gastrocnemius muscle. They reasoned that a primary block in glycogen synthesis (e.g., resulting from decreased glycogen synthase) would lead to increased glucose-6-phosphate levels, whereas if the decreased flux of glucose to glycogen reflected impaired glucose transport and/or phosphorylation, then glucose-6-phosphate levels would be low. They found a lower steady-state glucose-6-phosphate concentration in type 2 diabetics, indicating that the reduced rate of glycogen synthesis was secondary to impaired glucose transport, hexokinase activity, or both. In additional muscle NMR studies, these investigators detected a very low intracellular free glucose concentration during hyperinsulinemic hyperglycemic clamp studies in both normal and type 2 diabetic patients. This finding strongly suggested that glucose transport is the rate-controlling step in insulin-stimulated muscle glycogen synthesis, indicating that decreased insulin-mediated glucose transport is the major defect in the muscle insulin resistance of type 2 diabetes.

**Skeletal Muscle Lipid Metabolism**

Increased free fatty acid flux is a consistent finding in type 2 diabetic patients, as well as in obese insulin-resistant nondiabetic subjects. This usually is accompanied by elevated circulating FFA levels, particularly in the postprandial state, and increased FFA uptake into skeletal muscle, as well as liver, can be a cause of decreased insulin sensitivity. After cellular uptake, FFAs are converted to long-chain fatty acyl CoAs (LCFA-CoAs), which can be transported into the mitochondria by carnitine palmitoyltransferases to undergo β oxidation (Fig. 41-9). If not transported into the mitochondria, LCFA-CoAs can be reesterified

![Diagram of fatty acid metabolism and insulin action in skeletal muscle or liver](https://via.placeholder.com/150)

**Fig. 41-9.** Fatty acid metabolism and insulin action in skeletal muscle or liver. Obesity results in an increased flux of free fatty acids into the circulation and uptake by the myocyte or hepatocyte. Activated fatty acids (i.e., fatty acyl-CoAs) are “metabolized” primarily via one of two pathways, oxidation or storage. When fatty acid flux exceeds the ability of these pathways to dispose of fatty acyl-CoAs, intermediaries of fatty acid metabolism (e.g., diacylglycerol (DAG), phosphatidic acid (PA), lysophosphatidic acid (LPA), ceramide) accumulate. In turn, these fatty acid intermediates can activate a number of different serine kinases that can negatively regulate insulin action. Ceramide can also impair insulin action through interactions with PKB/Akt. An inability to completely oxidize fatty acids through β-oxidation, which leads to an accumulation of acylcarnitines, has also been hypothesized to cause insulin resistance, although the precise mechanisms leading to insulin resistance are, to date, unknown. AGPAT, acyl glycerol-3-phosphate acyltransferase; PAP, phosphatidic acid hydrolyase; PA, phosphatidic acid. (From Schenk S, Saberi M, Olefsky JM: Insulin sensitivity: modulation by nutrients and inflammation, J Clin Invest 118:2992–3002, 2008.)
with glycerol-3-phosphate (G-3-P) to form phosphatidic acid (PA), which is converted to diacylglycerol (DAG) and then to triglycerides. When levels of fatty acyl CoAs (particularly palmitoyl CoA) are high, the ability of cells to oxidize or store this lipid intermediate may be limiting, which leads to increased conversion of fatty acyl CoA to ceramide. With increased uptake of FFA into the cell, intracellular levels of LCFA-CoAs and intermediates such as DAG, ceramide, and triglyceride are increased. Evidence exists to indicate that these fatty acid intermediates and metabolites can impair insulin signaling by activating inhibitory serine/threonine kinases such as JNK1, PKCθ, IKKβ, and MTOR/p70S6K. In turn, these inhibitory serine kinases phosphorylate IRS-1, impairing the ability of IRS-1 to propagate downstream insulin signaling. In addition, accumulation of ceramide has an additional effect of impairing AKT activation, thus further inhibiting insulin signaling.

When lipid synthesis and fatty acid (FA) oxidation become unbalanced, inadequate complete mitochondrial β oxidation exaggerates the accumulation of these lipid metabolites, potentiating insulin resistance. In contrast, enhanced complete mitochondrial fatty acid oxidation causes a decrease in intracellular levels of lipid intermediates, leading to greater insulin sensitivity. These pathways provide an important connection between abnormal intracellular lipid metabolism and insulin resistance.

Intramyocellular triglyceride content, measured by muscle biopsy or NMR spectroscopy, is increased in obesity and type 2 diabetes and is a strong predictor of insulin resistance in both animals and humans. It is likely that increased intramyocellular triglyceride content does not, by itself, impair insulin signaling, but acts as a marker of increased intracellular LCFA-CoAs, DAGs, and other lipid intermediates. A strong negative correlation has been demonstrated between whole-body insulin sensitivity, as determined by the glucose clamp, and the content of LCFA-CoAs and DAGs, as measured in muscle biopsy samples.

**Kinetic Defects in Insulin Action**

Although most quantitative assessments of in vivo insulin resistance report impaired insulin action based on steady-state measurements, kinetic defects in insulin action in obesity have been demonstrated. Thus, the rate of activation of the effect of insulin in stimulating glucose disposal is decreased, and the rate of deactivation of the effect of insulin is increased. Given that under physiologic postprandial conditions, insulin is secreted in a phasic rather than a steady-state manner, it is likely that kinetic defects in insulin action are of functional importance, and that steady-state measurements of insulin action underestimate the functional defect in insulin sensitivity. This has been demonstrated by measuring glucose disposal during phasic administration of insulin during a glucose clamp, designed to mimic the pattern of insulin secretion during oral glucose tolerance tests. Total insulin-stimulated glucose disposal during the “phasic” clamp was reduced by 64% in obese subjects compared with lean controls. This is greater than the 20% to 50% decrease in steady-state insulin-mediated glucose disposal that was observed in glucose clamp studies in these same subjects, confirming the functional importance of kinetic abnormalities in insulin action.

In summary, skeletal muscle insulin resistance in type 2 diabetes is associated with multiple defects in insulin signaling, glucose transport, and oxidative and nonoxidative glucose metabolism. It remains to be fully determined which defects are primary and which are secondary, but a decrease in insulin-stimulated GLUT4 translocation appears to be the fundamental defect that gives rise to the insulin-resistant state.

**Liver**

In addition to peripheral insulin resistance and abnormal β cell function, the third major physiologic defect in type 2 diabetes mellitus is dysregulation of hepatic glucose output. The liver plays a key role in carbohydrate metabolism by extracting glucose from the portal vein and hepatic artery, and by releasing glucose derived from glycolysis or gluconeogenesis into the hepatic vein.

**Hepatic Glucose Output**

After an overnight fast, normal basal glucose production rates are 1.8 to 2.2 mg/kg/min, with about 90% of the glucose that is released into the circulation coming from the liver. After glucose ingestion, HGO must be suppressed promptly to limit the rise in plasma glucose levels; as intestinal glucose delivery wanes, HGO rates must be restored to meet the obligatory glucose needs of tissues such as the brain. These changes in HGO are mediated largely by changes in insulin and counterregulatory hormones (predominantly glucagon). The rate of basal HGO is increased in both obese and nonobese type 2 diabetic patients, but not in subjects with IGT (Fig. 41-10A). The fasting plasma glucose level and HGO are closely correlated in type 2 diabetic patients (Fig. 41-10B), which indicates that the rate of basal glucose production by the liver directly modulates the level of fasting hyperglycemia in type 2 diabetes. Gluconeogenesis is the predominant source of HGO following an overnight fast, and most studies suggest that gluconeogenesis is increased in type 2 diabetes and is a consistent abnormality, and suppression of plasma glucagon levels by infusion of somatostatin lowers plasma glucose levels in both normal and type 2 diabetic subjects.

Hepatic glucose production can be suppressed completely by high physiologic or supraphysiologic insulin levels in type 2 diabetes, but the sensitivity of HGO to lower concentrations of insulin is reduced. This reduced insulin sensitivity also contributes to the overall increase in glucose production in these patients. The ability of insulin to suppress HGO may in part occur indirectly through suppression of adipose tissue lipolysis and plasma FFA levels. Thus, impaired insulin-induced suppression of HGO in type 2 diabetes may in part be secondary to impaired inhibition of plasma FFA levels by insulin.

Finally, increased flux of gluconeogenic precursors and FFAs from peripheral tissues to the liver may participate in the maintenance of increased HGO in type 2 diabetes. Alanine, lactate, and glycerol production rates are increased in type 2 diabetes with fasting hyperglycemia, and increased plasma lactate and glycerol levels would be expected to promote gluconeogenesis. In obese type 2 diabetic patients, increased plasma FFA levels may stimulate gluconeogenesis and contribute to higher rates of HGO.
In summary, inhibition of glucose production and release is the major effect of insulin on hepatic glucose balance. In type 2 diabetes, the liver overproduces glucose in the basal state, primarily because of increased glucogenesis, and this is the predominant cause of fasting hyperglycemia. The metabolic milieu in this disorder is ideal for sustaining this abnormality. Exaggerated hormonal stimulation is provided by increased glucagon levels (in combination with hepatic insulin resistance), and augmented glucogenic precursor flow ensures adequate substrate availability. Finally, elevated FFA levels promote the gluconeogenic process. Decreased HGU has been reported in type 2 diabetes, and this contributes to postprandial hyperglycemia. It is likely that mechanisms for decreased HGU are comparable with the defects that cause hepatic insulin resistance and increased gluconeogenesis.

**Mechanisms of Hepatic Insulin Resistance**

Various defects in the cellular actions of insulin have been described in livers of type 2 diabetic patients, or in relevant animal models, and, in most ways, these defects are similar to what is seen in skeletal muscle and other tissues. These include a decrease in insulin receptor tyrosine kinase activity, decreased IRS-1/PI3K signaling, and impaired activation of AKT. An important pathophysiologic element unique to the liver involves the transcriptional control of gluconeogenesis. Gluconeogenesis is finely controlled by a complex transcriptional network that allows the liver to adjust rapidly to changes in glucose need. Glucagon stimulates adenylcyclase activity, leading to increased intracellular cyclic adenosine monophosphate (AMP) levels, with activation of PKA and subsequent phosphorylation and activation of the nuclear transcription factor CREB. CREB is a master positive regulator of gluconeogenic gene expression and the effects of CREB are facilitated by two nuclear co-activators, TORC2 and CBP. In addition, PGC1α, FOXO1, and HNF4a positively activate the gluconeogenic program. It is important to note that TORC22, CBP, and FOXO1 are highly insulin regulated. Insulin-induced phosphorylation of these co-factors, through activation of AKT/PKCA, causes nuclear exclusion of these proteins with inhibition of gluconeogenesis. This provides the mechanism for the ability of insulin to downmodulate gluconeogenesis. Once the liver is insulin resistant, phosphorylation of these co-factors is impaired and high levels of nuclear TORC2, CBP, and FOXO1 exist, leading to increased gluconeogenesis. From a therapeutic point of view, controlled inhibition of hepatic gluconeogenesis is a highly valuable approach to the treatment of type 2 diabetes.

**Adipose Tissue**

**Adipokines**

As was noted earlier, adipose tissue represents the body’s largest endocrine organ. Indeed, adipose tissue is responsible for secretion of a large number of polypeptide factors, some of which are exclusively elaborated by adipocytes and are termed adipokines. Some of the major adipokines include leptin, adiponectin, and resistin.

Adiponectin is secreted by adipocytes and circulates as a large multimeric protein complex consisting of up to 18 monomers. Two receptors for adiponectin have been identified (Adipo-R1 and Adipo-R2) with somewhat different tissue expression patterns. Adipo-R1 is more highly expressed in liver, whereas Adipo-R2 is predominant in muscle. Through these receptors, adiponectin stimulates AMP kinase activity, leading to a variety
of cellular effects that all serve to improve tissue insulin sensitivity. Thus, adiponectin is a bona fide insulin-sensitizing hormone and may play an important role in pathophysiologic states. For example, adiponectin levels are usually decreased in obesity and other insulin-resistant states, and circulating high-molecular-weight adiponectin levels are inversely correlated with the magnitude of insulin resistance. Furthermore, administration of adiponectin to animals leads to improvement in insulin sensitivity. Treatment of animals and insulin-resistant humans with insulin-sensitizing thiazolidinediones leads to an increase in adiponectin secretion from adipocytes, consistent with a role for increased adiponectin in the insulin-sensitizing effects of this class of therapeutics.

Resistin is another adipokine, and although it is much less well studied than adiponectin, previous reports suggest that resistin leads to a decrease in insulin sensitivity, and elevated levels of resistin may track with insulin-resistant states. Leptin is perhaps the best known of the adipokines, and it exerts its effects largely by reducing food intake and increasing thermogenesis. Obviously, in so far as leptin helps to control body weight, it has a profound effect on obesity-induced insulin resistance. Independent of its effects on obesity, some evidence indicates that leptin may directly improve insulin sensitivity, although this is less certain and requires further investigation. This is an interesting and evolving field, and a number of other adipokines have been identified that have effects on diverse physiologic systems.

Impact of Regional Fat Distribution and Adipocyte Size

Adipose tissue is responsible for only a small fraction of overall whole-body glucose disposal. Although glucose uptake per kilogram of tissue is reduced in insulin-resistant states, overall glucose disposal in adipose tissue probably is not significantly altered, given the expanded fat mass in most insulin-resistant subjects. Intraperitoneal (visceral) adipose tissue may be particularly deleterious to glucose homeostasis. Because of its anatomic location, visceral fat drains directly to the liver via the portal vein, thereby exposing the liver to high concentrations of FFA from this depot. Furthermore, visceral adipocytes appear to be more responsive to catecholamine-stimulated lipolysis and less responsive to suppression of lipolysis by insulin. It has long been recognized that excess fat in the upper part of the body (central or abdominal), termed android obesity, is associated with increased risk for type 2 diabetes, dyslipidemia, and increased mortality compared with lower-body (glucafemoral), or gynoid, obesity. Although the relationship between visceral fat and cardiovascular risk has been established, the association of insulin sensitivity with visceral versus subcutaneous truncal adipose tissue remains controversial. Visceral fat area, as determined by computed tomography scan, is correlated with decreased insulin action, as measured by the glucose clamp. On the other hand, with the use of similar techniques, the total volume of subcutaneous truncal adipose tissue was reported to be a better predictor of insulin resistance than was visceral fat. Because subcutaneous truncal adipose tissue contributes a greater quantity of overall FFAs to the systemic circulation than does visceral fat, it might have a more important influence on peripheral insulin action.

Subjects with deficiency of adipose tissue amount (lipoatrophy) or distribution (lipodystrophy) are also insulin resistant, with excess triglyceride deposition in skeletal muscle and the liver. In a transgenic animal model with absence of white adipose tissue, insulin resistance is associated with lipid deposition in skeletal muscle and liver—a phenotype that can be reversed by surgical implantation of normal adipose tissue. These findings suggest that adipose tissue plays a pivotal role in buffering of fatty acid flux, with insufficient buffering leading to “ectopic triglyceride” storage in muscle and the liver, resulting in deleterious metabolic effects. The more common scenario, however, is of excess adipose tissue in obesity; in this situation, the antilipolytic effects of insulin are impaired. This could result in increased FFA flux into muscle and liver, contributing to the increased intramyocellular and hepatic triglyceride content and insulin resistance observed in this condition.

Another aspect of lipid metabolism that influences insulin action is that of adipocyte size. Larger adipocytes are more resistant to insulin-stimulated glucose uptake and to insulin suppression of lipolysis and larger subcutaneous adipocytes may predict the development of type 2 diabetes, independent of insulin resistance. Smaller fat cells may be more efficient at fatty acid uptake and better able to buffer lipid flux. Indeed, it has been hypothesized that failure of adipogenic precursor cells to differentiate into adipocytes results in glucose intolerance, which may be due to inefficient handling of lipid flux by the remaining large adipocytes.

Inflammatory Pathway Activation and Insulin Resistance

In recent years, the concept has emerged that chronic, low-grade activation of proinflammatory pathways within insulin target tissues is an important cause of obesity-related insulin resistance. Thus, for many years, it has been known that elevated levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)α and interleukin (IL)-6, as well as C-reactive protein (CRP), exist in patients with type 2 diabetes mellitus and insulin resistance. Activation of intracellular inflammatory pathways within myocytes, hepatocytes, or adipocytes involves increased expression and/or activity of several serine kinases such as JNK1, IKKβ, and PKCθ, all of which can inhibit insulin action. Consistent with this, neutralization of TNFα improves insulin sensitivity in obese rodents, and genetic knockout or chemical inhibition of JNK1 or IKKβ improves insulin sensitivity in various mouse models. Perhaps more important, salicylates are well-known anti-inflammatory compounds that inhibit the IKKβ/NFκB pathway, and treatment of insulin-resistant rodents and type 2 diabetic patients with these agents leads to improved insulin action with a corresponding reduction in hyperglycemia.

The expanding adipose tissue mass in obesity and type 2 diabetes is a central focus for this chronic tissue inflammatory response. Activation of adipose tissue inflammatory pathways leads to a variety of adverse metabolic changes, including (1) increased lipolysis with elevated circulating FFA levels, (2) release of cytokines, which can impair insulin action, and (3) changes in the mix of adipokines (e.g., decreased adiponectin and increased resistin levels); all of these factors can impair insulin sensitivity.

Chronic inflammation in the liver can be a cause of hepatic insulin resistance. Thus, in obese and insulin-resistant states, inflammatory pathways are activated in liver tissue, with increased JNK1, IKKβ, and PKCθ activity, and these serine kinases blunt insulin signaling in hepatocytes. Attenuation of insulin action
results in increased levels of gluconeogenesis and glycogenolysis and elevated hepatic glucose production rates. In obese subjects, this situation often is accompanied by steatosis or steatohepatitis.

It is likely that this chronic inflammatory process contributes to skeletal muscle insulin resistance through changes in circulating concentrations of adipokines, or cytokines released from adipose tissue and/or liver. In addition, adipose tissue is interspersed within skeletal muscle, and these intermuscular adipose depots are increased in obese patients. This intermuscular adipose tissue contains macrophages and other immune cells, and the numbers of these cells are increased in obesity. It is possible that cytokines released by these immune cells could have local paracrine effects that contribute to skeletal muscle insulin resistance.

Although low-grade, chronic tissue inflammation can cause insulin resistance in obese and type 2 diabetic subjects, how does this inflammatory process begin? One possibility is that nutrient overload of adipocytes and liver initiates stress pathways, which activate some of the serine kinases (JNK1, IKKβ) that inhibit insulin action. Another important possibility relates to tissue macrophages. In obesity, the content of tissue macrophages is increased in adipose tissue and liver (Kupffer cells). These immune cells are highly proinflammatory and release a variety of cytokines, which act in a paracrine fashion on neighboring insulin target cells to cause insulin resistance. In this scenario, the chronic obese and type 2 diabetic state leads to chronic accumulation of activated tissue macrophages, which, in turn, release inhibitory cytokines that act locally in a paracrine fashion, thus contributing to the overall insulin-resistant state.

Other Contributors to the Insulin-Resistant Phenotype

**INSULIN-MEDIATED VERSUS NON-INSULIN-MEDIATED GLUCOSE UPTAKE**

Under basal conditions, a near steady state of glucose flux is approximated, and the rate of glucose appearance (HGO) equals the overall rate of glucose disposal. To understand the significance of increased basal HGO in type 2 diabetes, it is important to distinguish between insulin-dependent and insulin-independent processes of glucose disposal. By definition, insulin-mediated glucose uptake (IMGU) occurs in insulin target tissues under the influence of insulin. Non-insulin-mediated glucose uptake (NIMGU) consists of all glucose uptake that is not under the influence of insulin, and this has two components. NIMGU occurs in tissues (primarily the central nervous system) that are not targets for insulin action; it also involves insulin target cells and comprises the basal rate (non–insulin mediated) of glucose disposal by these tissues. Total glucose disposal (Rd) equals the sum of NIMGU and IMGU. NIMGU can be assessed in vivo by measuring Rd under conditions of severe insulinopenia induced by an infusion of somatostatin. Thus, after measurement of basal Rd (at basal or fasting insulin and glucose levels), somatostatin is administered to inhibit insulin secretion to negligible levels. Rd gradually falls to a new steady state that equals NIMGU because insulin action is absent under these conditions. With this approach, the proportion of basal Rd that is NIMGU is approximately two thirds in normal individuals at euglycemia and in type 2 diabetic subjects studied at their basal level of hyperglycemia. This means that at all levels of basal glycemia (normal and diabetes), most of the glucose is disposed of by NIMGU mechanisms, and the elevated rates of basal HGO that prevail in type 2 diabetes are associated with increased rates of NIMGU.

**PATHOPHYSIOLOGY OF FASTING VERSUS POSTPRANDIAL HYPERGLYCEMIA**

Once type 2 diabetes develops, peripheral insulin resistance, impaired insulin secretion, and increased HGO all contribute to lasting hyperglycemia, but increased HGO predominates. This conclusion derives from the known physiology of glucose homeostasis in the basal state. Thus, in the postabsorptive fasting state, insulin levels are low, and approximately 70% of basal glucose uptake (Rd) is non–insulin mediated in both normal and hyperglycemic type 2 diabetic subjects. Because skeletal muscle accounts for only 15% to 20% of basal glucose Rd, it follows that an impairment in insulin-mediated glucose uptake by muscle will have little effect on overall basal glucose Rd or on the fasting plasma glucose level. Major increases in fasting glucose levels do not occur unless the rate of glucose entry into the systemic circulation (Ra) increases, and in the basal state, glucose Ra essentially equals HGO. In type 2 diabetes, increases in glucose Ra readily lead to increases in fasting glucose levels because, in the setting of peripheral insulin resistance and impaired insulin secretion, the ability of IMGU to rise and accommodate an increase in Ra is severely curtailed. To illustrate, if basal Ra = Rd = 2 mg/kg/min at euglycemia and basal NIMGU = 1.4 mg/kg/min (70%) with a basal IMGU of 0.6 mg/kg/min (30%), a modest increase in HGO to 2.6 mg/kg/min would require doubling of IMGU (to 1.2 mg/kg/min) to maintain Rd = Ra (HGO) at euglycemia. Because type 2 diabetic subjects are insensitive to insulin, a much larger increase in insulin secretion would be necessary to produce euglycemia than in normal individuals. Because insulin secretion is impaired in type 2 diabetes, the ability of a type 2 diabetic subject to increase IMGU in response to a rise in Ra is greatly restricted. Instead, to raise Rd to the level of the new Ra and bring the system back into balance, the fasting glucose level must rise until Rd increases by mass action and equals Ra. This line of reasoning is strongly supported by the available data, which demonstrate close direct relationships between fasting plasma glucose levels and basal HGO in large groups of type 2 diabetic subjects under a variety of conditions. Thus, decreased insulin secretion and action provide the setting that allows glucose Ra to regulate fasting plasma glucose, leading to the principle that fasting hyperglycemia is largely due to increased HGO.

The cause of postprandial hyperglycemia, however, is more complex. Thus, in the postprandial state, glucose Ra comes predominantly from ingested carbohydrate, which enters the peripheral circulation. In the postprandial state, IMGU normally predominates, and the limited ability of type 2 diabetic subjects to increase IMGU (because of insulin resistance and impaired insulin secretion) allows the marked postprandial glucose excursions.

The clinical implications of this understanding of the pathophysiology of fasting versus postprandial hyperglycemia are obvious. Any form of antidiabetic therapy must address both aspects of hyperglycemia to be fully effective, which means that a given treatment modality must correct the disordered hepatic glucose metabolism at the same time that it improves insulin-mediated skeletal muscle glucose uptake. This principle is true for single modes of therapy (insulin, oral agents, weight loss) and for various combination forms of treatment. For example, a
treatment modality that lowers HGO combined with one that enhances IMGU would be an effective overall management strategy for controlling overall glycemia in type 2 diabetes.

GASTROINTESTINAL INCRETINS AND INTESTINAL BYPASS SURGERY

Incretins

An incretin is a gastrointestinal hormone that increases insulin release from the β cell in response to a meal or an oral glucose load. The “incretin effect” was first suggested following the observation that an oral glucose load stimulates insulin secretion to a significantly higher degree than does intravenous glucose. In subjects with type 2 diabetes mellitus, this incretin effect is greatly diminished, suggesting that this may play a significant role in the pathogenesis of type 2 diabetes mellitus.196

Although many peptides produced in the stomach and/or small intestine have a role in the regulation of food intake, the two dominant gut-derived incretins are GIP and GLP-1. GIP is secreted from enteroendocrine cells (“K cells”), which have highest density in the duodenum but are found throughout the small intestinal mucosa.189 Secretion of GIP is stimulated by carbohydrates and by lipids, and a 10- to 20-fold elevation in plasma concentration is seen following a meal. The GIP receptor is a Gαs-coupled G protein coupled receptor (GPCR), and activation leads to enhanced insulin secretion. GLP-1 is derived from the polypeptide product of the glucagon gene through a process of differential proteolytic cleavage within intestinal “L cells.”190 GLP-1 secretion is stimulated by the presence of nutrients in the gut lumen (predominantly distal small intestine and colon), and its secretion is highly correlated with insulin release. Similar to GIP, it interacts with a Gαs-coupled GPCR on β cells and is a potent insulin secretagogue.

In subjects with type 2 diabetes mellitus, GIP levels appear to be unchanged, whereas a pronounced defect in GLP-1 secretion is noted.197 It is interesting to note that type 2 diabetic subjects have a pronounced resistance to exogenous GIP infusion but have a normal response to GLP-1 infusion.192,193 Novel incretin-based treatment agents have focused on reducing the metabolism of endogenous GLP-1 and GIP through inhibition of dipeptidyl peptidase 4 (DPP-4), or through agonism of the GLP-1 receptor.194

Intestinal Bypass Surgery

Gastric bypass surgery is used increasingly for the treatment of morbid obesity. Over the years, clinical observations have demonstrated that morbidly obese type 2 diabetic patients undergoing bypass surgery exhibit rapid (within days) resolution of the diabetic state even before significant weight loss occurs. This rapid resolution of hyperglycemia has been reported within days after several types of upper intestinal bypass surgery, including Roux-en-Y gastric bypass, duodenal-jejunal bypass, and ileal transposition. This rapid insulin-sensitizing effect is not seen with adjustable gastric banding or with caloric restriction alone, both of which typically have a more delayed onset of effect. Although some differences in technique exist, bypass surgeries have in common the anatomic displacement of the duodenum and the proximal jejunum. Based on this, two competing hypotheses have emerged to describe the mechanisms underlying glucose normalization in response to these surgeries.195 The “foregut hypothesis” states that intestinal bypass surgery removes an as yet unidentified diabetogenic factor that is present in the bypassed duodenal/jejunal segment. The “hindgut hypothesis” states that increased/rapid delivery of food to the distal jejunum and ileum (hindgut) directly stimulates secretion of an antidiabetic factor, possibly GLP-1.

Although limited, recent experimental data in rats seem to support the foregut hypothesis in this model. In the Goto-Kakazaki rat model of lean type 2 diabetes, duodenal-jejunal bypass surgery led to improved insulin sensitivity, independent of GLP-1 levels. Further, reoperation to reestablish duodenal continuity with the stomach led to return of diabetes, even in animals in which a second bypass conduit was created to simultaneously induce rapid nutrient passage to the distal small intestine.193 Conversely, in obese human subjects undergoing Roux-en-Y gastric bypass, GLP-1 levels were increased within 2 days postoperatively, and this elevation was correlated with reduced appetite.196

Syndromes of Severe Insulin Resistance

Some patients demonstrate a severe degree of resistance to endogenous or exogenous insulin. These patients may require extremely high treatment doses of insulin to normalize blood glucose levels and represent a clinically distinct group designated as having “severe insulin resistance.”197 Definitive laboratory values to designate the presence of severe insulin resistance have not been agreed upon, although fasting insulin levels above 50 to 70 µU/mL or peak (post–oral glucose tolerance test [OGTT]) insulin levels above 350 µU/mL may be acceptable diagnostic thresholds.198 In addition to insulin resistance, certain clinical features are often present with many of these syndromes, including acanthosis nigricans and, in women, symptoms of ovarian hyperandrogenism.

LIPOATROPHIC DIABETES

Loss of subcutaneous fat (lipoatrophy)190 can be associated with severe insulin resistance. The mechanism underlying insulin resistance in these conditions is multifactorial, related to ectopic deposition of triglycerides in peripheral tissues, increased circulating lipid metabolites such as free fatty acids, and decreased levels of adipokines (adipose-derived hormones) such as adiponectin and leptin. Although all lipoatrophic syndromes are associated with insulin resistance to a degree, the severity of metabolic disturbance generally is correlated with the extent of adipose tissue loss. In this regard, severe insulin resistance refractory to insulin therapy may be seen in syndromes of generalized lipoatrophy but are unusual with partial lipoatrophy.

The most common cause of lipoatrophy is that associated with antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection. However, many other disease states may present with partial or generalized lipoatrophy, and these may in turn be acquired conditions or may have a genetic basis. The topics of lipoatrophy and lipodystrophy are covered comprehensively in Chapter 38.

DEFECTS IN INSULIN RECEPTOR SIGNALING

Type B Insulin Resistance

Patients with type B resistance have extreme levels of insulin resistance associated with the presence of anti-insulin receptor antibodies.200 First described in 1975, patient-derived serum and serum immunoglobulins may block insulin binding in a variety of tissues and subjects.201 As with other autoimmune disorders, this condition is seen more commonly in women, and among
ethnic groups is most common in blacks. Mean age of onset is 40, but reported cases have ranged from ages 12 to 78.

The main clinical features include hyperglycemia, acanthosis nigricans, and clinical signs of autoimmunity. These may include leukopenia; increases in antinuclear antibody, erythrocyte sedimentation rate, and serum immunoglobulin (IgG); proteinuria; alopecia; arthritis; vitiligo; Raynaud’s phenomenon; and enlarged salivary glands. Insulin resistance may be extreme, with patients requiring >1000 U/day. However, some patients may present with postprandial hyperglycemia coupled with fasting hyperglycemia, or isolated fasting hyperglycemia. In cases with hyperglycemia, insulin levels may be elevated as a result of an antibody-induced reduction in insulin clearance, and this may be confused with insulinoma. Hypoglycemia may be due in part to antibody-mediated activation of insulin receptor (IR) signaling.

The clinical course can be variable, ranging from persistent hyperglycemia not amenable to insulin treatment to spontaneous remission months to years after disease onset. Patients have rarely progressed from severe insulin resistance to severe hypoglycemia over several weeks to months. Glucocorticoids and/or plasmapheresis may be useful therapy in severe cases.

The dominant site for antibody binding is a limited region in the receptor β subunit between amino acid residues 450 and 601. Although initial studies demonstrated that insulin receptor antibodies blocked insulin binding to its receptor in a wide variety of tissues from several species, the biological activity of insulin receptor antibodies is complex. Virtually all antibodies isolated from hyperglycemic or hypoglycemic patients acutely stimulate insulin receptor activity, such as glucose uptake and metabolism. Over time, cells become refractory to these effects, and this may underlie the clinical heterogeneity of this syndrome.

**Type A Insulin Resistance**

This clinical definition is applied to individuals with severe, apparently inherited insulin resistance, in the absence of growth defects or lipodystrophy. The most common features are the peripubertal onset of insulin resistance and acanthosis nigricans and, in women, symptoms of ovarian hyperandrogenism. Body habitus is varied but can be accompanied by prominent musculature, which may result from hyperandrogenism or from insulin-induced anabolism via the insulin-like growth factor (IGF)-1 receptor. Many of these patients harbor heterozygous mutations in the insulin receptor gene or have homozygous mutations that cause relatively mild defects in receptor function. Mutations may be associated with impaired binding of insulin to cells and tissues from affected patients; or with normal insulin binding but impaired receptor tyrosine kinase activity. The syndrome may display autosomal dominant or recessive inheritance. Other patients with clinical type A insulin resistance syndrome do not have mutations in the insulin receptor gene and may have as yet unidentified mutations in downstream intracellular signaling molecules.

**Other Congenital Syndromes of Insulin Receptor Signaling**

1. Leprechaunism (Donohue’s syndrome): First described in 1954 in two siblings with intrauterine and postnatal growth retardation, sparse subcutaneous fat, acanthosis nigricans, and early death. Patients have characteristic facies with large ears and micrognathia. Fasting hyperglycemia and marked hyperinsulinemia are always present, and survival past the first year is uncommon. The precise molecular defect in leprechaunism is not known; however, insulin binding to cells is markedly reduced and inactivating mutations in the insulin receptor locus have been reported.

2. Rabson-Mendenhall syndrome: A clinical syndrome that includes severe insulin resistance and acanthosis. Patients present with characteristic features of short stature, protruberant abdomen, abnormal dentition and nails, and pineal hyperplasia. Insulin binding is reduced, which may be associated with reduced receptor synthesis. This in turn is due to impaired cleavage of the insulin proreceptor, which is associated with a point mutation that affects the proteolytic cleavage site. The degree of insulin resistance is intermediate between that seen with leprechaunism and type A insulin resistance.

3. Pseudoacromegaly: Severe insulin resistance associated with pathologic tissue growth similar to that seen in acromegaly, but with normal IGF-1 and growth hormone (GH) levels. The initial report from Flier et al. in 1993 described a 19-year-old patient with acromegoid features, a history of accelerated linear growth, and a normal GH/IGF-1 axis. The patient was found to have severe fasting hyperinsulinemia and lacked a hypoglycemic response to an IV insulin bolus. Cultured skin fibroblasts had normal insulin-stimulated mitogenic responses but displayed a marked reduction in insulin-stimulated glucose uptake. No functional insulin receptor or GLUT4 mutations were identified. Additional studies suggest that the defect resides in the activation of phosphoinositide-3-kinase. The acromegoid features seen in this syndrome are hypothesized to result from very high insulin levels coupled with the normal insulin anabolic and mitogenic signaling pathways. The genetic defect underlying this syndrome remains unknown. In a recent report, pericentric inversion of chromosome 11 segregated with acromegoid features in one family, although candidate genes affected by this inversion remain to be determined.

**DEFECTS RELATED TO THE INSULIN MOLECULE**

**Anti-insulin Antibodies**

The seminal studies of Berson and Yalow demonstrated the presence of anti-insulin antibodies, which caused insulin resistance in a series of insulin-treated patients. As a complication of insulin therapy, insulin resistance due to anti-insulin antibodies is associated with a very high antibody titer and was prevalent with the widespread intermittent use of beef- and pork-derived insulin of limited purity, containing proinsulin, C-peptide, and other peptide contaminants. Anti-insulin antibodies may develop in persons treated with human insulin as well but are associated with clinically significant insulin resistance to therapy only in rare instances. Immune insulin resistance tends to be self-limited; 50% of cases last less than 6 months, and 75% less than 1 year. Switching insulin preparations is considered the first line of treatment. In refractory cases, prednisone (60 to 80 mg/day for 2 to 3 weeks) has resulted in lower insulin requirements and on occasion has been associated with dramatic responses, including hypoglycemia.

Rare patients have been described who demonstrate antibodies in the absence of previous insulin therapy, a condition called the insulin autoimmune syndrome. This condition is associated with extremely high serum levels of endogenous insulin but...
normal serum levels of glucose and is usually seen in conjunction with other autoimmune diseases. The most frequent presentation is postprandial hypoglycemia.\textsuperscript{226}

**Increased Insulin Degradation**

Some patients demonstrate severe resistance to insulin administered subcutaneously but normal responses to insulin delivered intravenously or intraperitoneally. To account for this finding, it has been proposed that these patients have increased insulin-degrading enzyme (insulinase) activity in subcutaneous tissues. A previous attempt to directly demonstrate increased skin insulinase activity, or to directly measure the presence of insulin degradation products in skin from these patients, was not successful.\textsuperscript{227}

**Mutant Insulins**

Several families have been described in which one or more members have missense mutations in the insulin gene causing amino acid substitutions within the proinsulin molecule, leading to biologically defective insulin.\textsuperscript{228-235} All patients have marked fasting hyperinsulinemia or hyperproinsulinemia, but with normal glucose levels or with mild hyperglycemia. These patients respond normally to exogenous insulin and therefore are “insulin resistant” only to the endogenously produced hormone.

**Molecular Genetics of Type 2 Diabetes Mellitus**

Many lines of evidence indicate a strong genetic component to type 2 diabetes. Although acquired factors such as obesity might be necessary to bring out the phenotypic manifestation of type 2 diabetes, these alone are insufficient in most patients without a preexisting genetic determinant. Although type 2 diabetes shows clear familial aggregation, it does not segregate in classical mendelian fashion and therefore is likely to be a genetically heterogeneous, polygenic disease. In other words, more than one diabetes gene occurs within a population, and it is possible that more than one abnormal genotype must exist within an individual for the type 2 diabetic phenotype to develop. For example, it is possible that one or more genes involved in insulin action are affected, along with a separately inherited genetic defect that is responsible for the loss of β cell function that occurs late in the course of development of type 2 diabetes.

Several strategies have been employed to search for type 2 diabetes susceptibility genes. In the candidate gene approach, the investigator develops a hypothesis that a certain gene may be involved in the pathogenesis of type 2 diabetes mellitus. The sequence of this candidate gene is then compared in normal and type 2 diabetic subjects to look for structural abnormalities in the disease state. A second approach involves genome-wide association (GWA) studies. GWA studies make use of randomly distributed polymorphic genetic markers, such as single nucleotide polymorphisms (SNPs), to map the location of the disease phenotype to a particular chromosomal locus. This goal is accomplished by determining whether the DNA markers co-segregate with the type 2 diabetes phenotype in a pedigree or population with sufficient numbers of affected individuals.

Type 2 diabetes is polygenic and multifactorial, and, in addition to genetic factors, the environment (obesity, physical inactivity, diet) modulates the diabetic phenotype. Because of this, accurate clinical and metabolic phenotyping is critical in attempting to determine the role of individual genes in this disease.

**Candidate Gene Approach**

Most candidate gene studies have focused on genes that encode proteins in the pathways of pancreatic β cell insulin secretion, or insulin signal transduction. Many studies in this regard have been undertaken, and lack of reproducibility has limited their interpretation. Earlier studies in this area had problems with poor matching of cases and controls, testing of a limited number of markers per gene, and small study population size with consequently little power to detect genuine effects. As a result, few associations have been replicated in additional populations.\textsuperscript{236} Several studies examined the insulin receptor, glycogen synthase, and GLUT4 as potential candidate genes in type 2 diabetes. Except in rare individuals, the primary sequences of these genes are normal, eliminating them as diabetes gene loci. In some populations, IRS-1 variants may be two to three times more common in patients with type 2 diabetes than in normal subjects, and in some studies, an association has been found between polymorphisms affecting the region of IRS-1 important for PI3K binding and a reduction in insulin sensitivity,\textsuperscript{237} although not all studies have confirmed this association.\textsuperscript{238}

**Genome-Wide Association Studies**

Because the candidate gene approach was not productive in identifying type 2 diabetes mellitus genes, it was largely supplanted by genome-wide association (GWA) studies involving linkage analysis.\textsuperscript{239} In a GWA study, DNA samples are obtained from two groups of participants: subjects with disease, and matched subjects without disease. The genomes then are scanned for markers of genetic variation such as SNPs. If specific genomic markers are more frequent in subjects with the disease phenotype, they are termed disease-associated. These markers then can be used to direct researchers to specific chromosomal loci, and positional cloning techniques are used to identify the specific gene. However, initial attempts at performing GWA studies to identify major susceptibility loci in type 2 diabetes were limited by the prohibitive technical (e.g., there are \(\approx 10\) million common SNPs) and financial hurdles involved in studying the large populations needed to attain sufficient power to detect the small effects of individual genes.

Recent advances have greatly increased the power of GWA studies to detect disease susceptibility alleles/haplotypes. Dense genotyping chips, containing sets of hundreds of thousands of SNPs that provide coverage of much of the human genome, are now available, so that for the first time, GWA studies of thousands of cases and controls are feasible. Most important has been the development of the International HapMap resource.\textsuperscript{240-242} The HapMap is based on the idea that the human genome can be organized into haplotype blocks, that is, sizable regions of DNA over which little evidence for historical recombination has been found (all SNPs found within a haplotype are inherited together as a group owing to their proximity to each other, rather than inherited randomly, as occurs with recombination). Within each haplotype block, a “tag SNP” has been identified that uniquely identifies that haplotype. The number of tag SNPs that contain most of the information about the patterns of genetic variation is estimated to be 300,000 to 600,000—far fewer than the 10 million common SNPs. Thus, these haplotype frameworks provide substantial statistical power in studies of common genetic variation, and the construction of a haplotype map of the human genome has greatly facilitated comprehensive genetic association studies of human disease.
Table 41-1. Confirmed T2DM Susceptibility Variants

<table>
<thead>
<tr>
<th>Representative SNP</th>
<th>Chromosome</th>
<th>Position of SNP</th>
<th>Ancestral Allele</th>
<th>SNP Allele</th>
<th>Gene</th>
<th>Combined OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs8050136</td>
<td>16</td>
<td>52373776</td>
<td>A</td>
<td>C</td>
<td>FTO</td>
<td>1.17 (1.12–1.22)</td>
<td>1.3 × 10^{-12}</td>
</tr>
<tr>
<td>rs10946398</td>
<td>6</td>
<td>20769013</td>
<td>C</td>
<td>A</td>
<td>CDKAL1</td>
<td>1.12 (1.08–1.16)</td>
<td>4.1 × 10^{-11}</td>
</tr>
<tr>
<td>rs5015480</td>
<td>10</td>
<td>94455539</td>
<td>C</td>
<td>T</td>
<td>HHEX</td>
<td>1.13 (1.08–1.17)</td>
<td>5.7 × 10^{-10}</td>
</tr>
<tr>
<td>rs1111875</td>
<td></td>
<td>94452862</td>
<td>C</td>
<td>T</td>
<td></td>
<td>1.14 (1.11–1.18)</td>
<td>8.6 × 10^{-10}</td>
</tr>
<tr>
<td>rs10811661</td>
<td>9</td>
<td>2214094</td>
<td>C</td>
<td>T</td>
<td>CDKN2B</td>
<td>1.20 (1.14–1.25)</td>
<td>7.8 × 10^{-15}</td>
</tr>
<tr>
<td>rs564398</td>
<td>9</td>
<td>22019547</td>
<td>T</td>
<td>A</td>
<td>CDKN2B</td>
<td>1.12 (1.07–1.17)</td>
<td>5.1 × 10^{-15}</td>
</tr>
<tr>
<td>rs4402960</td>
<td>9</td>
<td>186994389</td>
<td>G</td>
<td>T</td>
<td>IGF2BP2</td>
<td>1.14 (1.11–1.18)</td>
<td>1.3 × 10^{-15}</td>
</tr>
<tr>
<td>rs1326634</td>
<td>8</td>
<td>11825396</td>
<td>C</td>
<td>T</td>
<td>SLC3A2</td>
<td>1.12 (1.07–1.16)</td>
<td>1.7 × 10^{-15}</td>
</tr>
<tr>
<td>rs7901695</td>
<td>10</td>
<td>114744078</td>
<td>C</td>
<td>T</td>
<td>TCF7L2</td>
<td>1.37 (1.31–1.43)</td>
<td>1.0 × 10^{-15}</td>
</tr>
<tr>
<td>rs5215</td>
<td>11</td>
<td>17365206</td>
<td>T</td>
<td>C</td>
<td>KCNJ11</td>
<td>1.14 (1.10–1.14)</td>
<td>5.0 × 10^{-11}</td>
</tr>
<tr>
<td>rs1801282</td>
<td>13</td>
<td>12368125</td>
<td>C</td>
<td>G</td>
<td>PPARγ</td>
<td>1.14 (1.08–1.20)</td>
<td>1.7 × 10^{-4}</td>
</tr>
</tbody>
</table>

Adapted from ref. 247.
Representative SNPs (RS) are shown for each signal, with odds ratios (ORs) and 95% confidence intervals (CIs) reported with respect to the risk allele (denoted in bold).
An OR of 1 denotes no difference in diabetes cases among those having the risk allele and those who do not. SNPs selected for inclusion are those with the strongest association in U.K. data sets. In the case of HHEX, data are combined from rs5015480 and rs1111875 (r² = 1 in HapMap CEU). Combined estimates of ORs were calculated by weighing the log ORs of each study (UK, DGI, FUSION) by the inverse of their variance.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

MODY refers to disorders due to monogenic defects in β cell function, with little or no defect in insulin action. They usually are transmitted as an autosomal dominant trait and are characterized by the onset of overt diabetes, usually before 25 years of age. The MODY phenotype is associated with abnormalities in glucose-6-phosphate, glucokinase is thought to play a key role in the “glucose sensor” of the β cell. Impaired hepatic glucose phosphorylation also may contribute to hyperglycemia in patients with MODY-2. It is interesting to note that most subjects with glucokinase mutations have very mild hyperglycemia, a normal first-phase insulin response to intravenous glucose, and a non-progressive course. MODY-3 is the most common subtype. It is associated with mutations on chromosome 12 in a gene encoding HNF-1a, a liver transcription factor that also is expressed in β cells. In contrast to patients with MODY-2, hyperglycemia in patients with MODY-3 tends to be progressive. Because they frequently present in adolescence with symptomatic hyperglycemia, type 1 diabetes mellitus might be diagnosed. MODY-4 is due to mutations in yet another transcription factor gene, insulin promoter factor 1 (IPF-1), which in its homozygous form leads to total pancreatic agenesis. Additional mutations have more recently been described that involve HNF-1b and NeuroD1/BETA2. In “garden variety” type 2 diabetes, mutations in the glucokinase and hepatic nuclear transcription factor genes are rare. Point mutations of IPF-1, however, have been associated with increased risk for type 2 diabetes.

Concluding Overview

With regard to the sequential development of type 2 diabetes, population-based and prospective studies indicate that insulin resistance is the initial defect, although in some populations, insulin secretory abnormalities may be primary. In a number of different ethnic groups, insulin resistance has been found to exist in the prediabetic state in the absence of any impairment in insulin secretion. Thus, insulin resistance and hyperinsulinemia characterize most individuals in whom type 2 diabetes is destined to develop. However, except in extreme cases, insulin resistance alone is not sufficient to cause the full-blown type 2 diabetic phenotype. Decreased β cell function eventually must supervene to cause the full-blown syndrome. This setting leads to the scheme depicted in Fig. 41-2, in which insulin resistance (genetic and/or acquired) leads to hyperinsulinemia and compensated glucose metabolism. Eventually, in some of these individuals, perhaps those with a coexisting genetically determined β cell defect, the ability of β cells to compensate by sustaining hyperinsulinemia declines, and insulin secretory defects appear, along with decreased β cell mass. At this stage, glucose
metabolism decompensates, and the hyperglycemic diabetic state emerges. This scheme (see Fig. 41–2) describes most patients, but because type 2 diabetes is a heterogeneous disease, this scenario may not apply to all.

Once type 2 diabetes has been established, the abnormal metabolic and hormonal milieu leads to secondary changes with worsening hyperglycemia. Thus, insulin resistance tends to be more marked in type 2 diabetes than in the prediabetic IGT state, and insulin secretion continues to decline throughout the course of established type 2 diabetes. Therefore, many patients, even if they initially are well controlled by diet or oral hypoglycemic agents, eventually require insulin for control of their diabetes. Glucotoxicity may well be the causal link here. Thus, strong evidence indicates that chronic hyperglycemia per se can lead to secondary worsening of both insulin resistance and insulin secretion, with the potential for a vicious cycle in which hyperglycemia begets more hyperglycemia. Support for this concept comes from numerous observations showing that control of hyperglycemia by insulin therapy, weight loss, or oral agents leads to improvements in both insulin secretion and insulin action. Obesity and aging, as well as other factors, are acquired conditions that can cause or contribute to insulin resistance and β-cell dysfunction.

Because of the convergence of primary and secondary events that coexist in the manifest type 2 diabetic state, it is a daunting task to identify the critical biochemical and cellular defects that underlie this disorder. Most likely, new insights will come from the field of molecular genetics. By finding genes that are abnormal in type 2 diabetes, we will be able to document cellular defects that initiate this syndrome. We also might find that different sets of genetic defects exist in different patients, and that, depending on other genetic or acquired features, they complement each other in different ways. Discovery of all the molecular defects that can lead to type 2 diabetes is an enormous but completely feasible goal and should provide the basis for an exciting future for our understanding of the causes and treatments of this disease.

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... just membrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation, J Biol Chem 272:29911–29918, 1997.


CHAPTER 41 — TYPE 2 DIABETES MELLITUS: ETIOLOGY, PATHOGENESIS, AND NATURAL HISTORY


