Insulin Secretary and Insulin Resistance Defects in Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (DM) accounts for at least 85% to 90% of all cases of diabetes in the United States. In recent decades, the number of people in the United States and throughout the developed world affected by type 2 DM has steadily climbed to the point of an epidemic, placing a staggering clinical and economic burden on modern society. The estimated worldwide prevalence of type 2 DM in 2001 was 150 million, and it has been estimated that this number may double by 2025. Fueling the diabetes epidemic is the rising incidence of obesity, food intake hypercaloric with regard to metabolic need, and sedentary lifestyle. These environmental factors play a contributory role in the development of type 2 DM, influencing expression of disease in genetically predisposed individuals.

Type 2 DM is a disease of complex pathogenesis, with a typically subtle onset and an inexorably slow progression. The study of the natural history of type 2 DM is complicated by the disease’s insidious, often asymptomatic onset and the fact that the most common inheritance pattern is polygenic. Nevertheless, the natural history has been mapped on a population basis and in susceptible families to the extent that we can define both subtle early defects and phenotypes at risk for type 2 DM. This allows identification of high-risk individuals who should be targeted for therapy early after the onset of disease—or even prior to disease onset, so as to delay or prevent the emergence of type 2 DM. Fortunately, an increasing array of pharmacotherapy options targeting specific pathophysiologic defects are available to help combat type 2 DM.

Despite the typically multifactorial inheritance, all forms of type 2 DM are defined by fasting and/or postprandial hyperglycemia caused by 2 definable defects: subnormal responsiveness to insulin (insulin resistance) in key sites of glucose homeostasis (including skeletal muscle, adipose tissue, and the liver) and an insulin secretory defect preventing otherwise compensatory insulin hypersecretion. Which of these defects comes first has been a topic of debate for several decades. Most of the available evidence favors the view that the ultimate triggering event is impaired insulin secretion, which, when superimposed on a background of impaired insulin action (insulin resistance), leads to overt type 2 DM. Nesher et al demonstrated that insulin resistance is neither necessary nor sufficient for the development of type 2 DM but, rather, that defective insulin secretion is the primary defect responsible for unmasking overt diabetes. Specifically, the study showed that while most patients with type 2 DM had some degree of insulin resistance, there were patients with a confirmed diagnosis of diabetes who had no evidence of insulin resistance. These individuals remained normoglycemic by compensating for the reduction in insulin sensitivity with increased insulin secretion. Therefore, insulin resistance alone is insufficient to cause type 2 DM. The development of overt type 2 DM must involve a defect in insulin secretion at the level of the beta cell that prevents compensatory insulin hypersecretion.

This manual is the first of a 2-part review of well-defined as well as newly identified pathogenetic mechanisms in type 2 DM. This half of the review examines in further depth the roles played by the dual defects of impaired insulin secretion (beta cell dysfunction) and subnormal insulin action (insulin resistance) and highlights the clinical implications of these defects. The discussion continues in the next manual with a review of the evolving knowledge of how gut-derived peptides (incretins) and adipocyte-derived cytokines (adipokines) influence insulin secretion and action in type 2 DM.

NORMAL GLUCOSE HOMEOSTASIS

GLUCOSE SOURCES AND PRODUCTION

The serum glucose concentration represents the net sum of glucose entering the circulation from endogenous or exogenous sources minus glucose removed from the circulation for storage or utilization (Figure 1). Exogenous glucose is derived solely from dietary food.
sources and absorbed from the gut. Gut-derived glucose results in an above-fasting glucose concentration for no longer than approximately 4 hours following a meal. Endogenous glucose sources include stored glucose released from liver glycogen (glycogenolysis). The liver stores approximately 80 g of glucose as glycogen, and once mobilized, the glycogen storage pool is virtually 100% depleted within 24 hours. The other important source of endogenous glucose is gluconeogenesis, which effectively recycles 3-carbon fragments of fat (glycerol), protein (alanine and glutamine), and carbohydrate (pyruvate and lactate) via the Cori cycle in the liver, where they are reassembled as glucose. Although gluconeogenesis usually is regarded as a hepatic process, with prolonged fasting, the kidney contributes as much as 20% to 25% toward gluconeogenesis.

**GLUCOSE UTILIZATION**

Glucose utilization is either insulin-dependent or insulin-independent. Insulin-dependent influences include uptake of glucose by muscle tissue, either for glycogen storage or for glycolysis, and glucose-to-glycerol conversion by adipose tissue and incorporation of glycogen and free fatty acid (FFA) as stored triglyceride. In the liver, insulin promotes action of glycogen synthase, thereby promoting hepatic glucose storage of glycogen. Equally important, insulin restrains hepatic gluconeogenesis. Non–insulin-dependent glucose utilization takes place in most other tissues—notably the formed elements of the blood, the kidneys, and brain tissue (neurons of the central nervous system [CNS]). Most glucose presented to the kidney as glomerular filtrate is reabsorbed in the proximal renal tubule, but at high concentrations (> 180–200 mg/dL), filtered glucose may exceed the renal T_{\text{max}} (maximum transport rate), with resultant spillage of glucose into the urine as glycosuria.

**HORMONAL INFLUENCES**

The most potent hormonal influence on glucose homeostasis is exerted by insulin, via its ability to promote glucose uptake and to restrain glycogenolysis and gluconeogenesis. Glucose counter-regulatory hormones oppose the effects of insulin, and in contrast to insulin (a largely stand-alone influence) have fourfold redundancy with regard to the number of hormones. The immediate defense against hypoglycemia is glucagon, which is released from pancreatic islet alpha cells in response to the decreasing blood glucose concentration; one of the immediate effects of glucagon is stimulation of hepatic gluconeogenesis. Epinephrine promotes lipolysis and gluconeogenesis, whereas cortisol and growth hormone antagonize cellular actions of insulin and promote muscle proteolysis so as to provide substrate for gluconeogenesis.

During fasting, low insulin levels result in increased glucagon secretion and permit endogenous glucose production by disinhibiting the processes of hepatic gluconeogenesis and glycogenolysis. Simultaneously, glycogen synthesis and glucose uptake by insulin-sensitive tissues are reduced. In the postprandial state, there is a simultaneous increase in serum insulin and reciprocal reduction in serum glucagon concentrations, leading to a reversal of these net processes. The competing processes of glucose production and glucose utilization are rarely “all or none” but rather simultaneous, with one simply predominating at a given moment in time, based on physiologic conditions. As a partial reflection of the normal tight control of blood glucose, glucagon, the dominant gluconeogenesis-promoting hormone, stimulates insulin release, whereas insulin simultaneously inhibits glucagon release.

**NORMAL INSULIN SECRETION AND ACTION**

**Insulin Secretion**

Insulin is secreted as a larger precursor molecule,
proinsulin, by the beta cells of the pancreatic islets. Postsecretory cleavage of proinsulin produces bioactive insulin and a 31-residue fragment known as C-peptide, which is essentially biologically inert but is a useful marker of endogenous insulin production.

Insulin secretion is regulated primarily by blood glucose concentration, although other nutrients and peptides, particularly alanine and glutamine, are also influential. After a meal, high blood glucose levels from intestinal digestion and absorption of carbohydrate directly stimulate insulin secretion. Evidence of postprandial insulin action includes increased glucose uptake by myocytes, FFA uptake and storage as triglyceride by adipose tissue, and storage of glucose as glycogen by the liver. Of equal importance, the insulin-rich postprandial state is also characterized by inhibition of stored fuel mobilization (ie, lipolysis, gluconeogenesis, and glycogenolysis) from peripheral sources.

Normally, insulin secretion in response to glucose is biphasic, with an early first phase followed by a second sustained phase (Figure 2). The first phase peaks 2 to 5 minutes following a glucose load and lasts approximately 10 minutes. This response is due primarily to the release of preformed secretory granules from the beta cell. The second, more prolonged phase involves release of newly synthesized insulin in response to glucose.

Glucose-stimulated secretion of insulin begins with glucose transport into the beta cell by the GLUT2 transporter (Figure 3). Glucose uptake by the beta cell is substrate-driven, at a rate determined by serum glucose concentration in the extracellular compartment and the amount of unmetabolized intracellular glucose within the beta cell. Thus, in the aggregate, glucose uptake by the beta cell is dependent on the extracellular/intracellular concentration gradient of glucose and on the integrity of the GLUT2 transporter. Once glucose enters the beta cell, it is metabolized via glycolysis. The resulting generation of adenosine triphosphate (ATP) causes cell membrane depolarization through the phosphorylation of an ATP-sensitive potassium channel, allowing entry of calcium ions into the cell. The rise in intracellular calcium signals release of insulin from secretory granules into the extracellular space, and from thence to the portal circulation. ADP = adenosine diphosphate; SUR = sulfonylurea receptor. (Adapted with permission from Powers AC. Diabetes mellitus. In: Jameson JL, editor. Harrison’s endocrinology. New York: McGraw-Hill Publishing Division; 2006:287. © 2006 The McGraw-Hill Companies, Inc.)

Insulin Action

After being secreted from beta cells, 50% of insulin is degraded by the liver. Insulin, after binding to its receptor, causes autophosphorylation and activation of signaling molecules. This causes translocation of
GLUT-4 to the cell’s surface, which is required for glucose uptake by skeletal muscle (Figure 4). In the setting of insulin resistance, reduced insulin-stimulated glucose uptake in adipocytes may occur due to down-regulation of GLUT-4 expression.

There are 2 families of cellular transporters of glucose: (1) sodium-linked transporters that actively transport glucose and (2) transporters that implement facilitated diffusion to move glucose. The diffusion group of transporters consists of 5 transmembrane proteins: GLUT-1, GLUT-2, GLUT-3, GLUT-4, and GLUT-5. Each GLUT protein has a distinct property and tissue distribution (Table 1). For practical purposes, the physiologically important GLUT transporters are GLUT2 (the transporter used by the beta cell to sense and respond to the ambient glucose concentration), GLUT-4 (the major insulin-responsive glucose transporter in skeletal muscle), and GLUT-3 (the major non-insulin-requiring, substrate-driven glucose transporter abundant in neuronal tissue).

**Figure 4.** Insulin–insulin receptor binding stimulates glucose transport in muscle cells. Binding of insulin to the insulin receptor activates a tyrosine kinase intrinsic to the internal domain of the insulin receptor; tyrosine phosphorylation of insulin receptor substrates activates phosphoinositide-3 kinase (PI3K), with downstream effects to promote glycolysis, glycogen storage, protein synthesis, and inhibition of proteolysis. Importantly, PI3K activation probably signals translocation of GLUT-4 glucose transporters from an inactive intracellular storage pool to active expression at the cell membrane. GLUT-4 binds to glucose in the extracellular environment and facilitates its entry into the cell. AMP = adenosine monophosphate; ATP = adenosine triphosphate; IRS = insulin-receptor substrate; p110, p85 = subunits of phosphoinositide-3 kinase; SH2 = Scr homology region 2. (Adapted with permission from Shepherd PR, Kahn BB. Glucose transporters and insulin action: implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:250. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

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**BETA CELL DYSFUNCTION IN TYPE 2 DIABETES**

**THE PREDIABETIC STATE**

Compensatory Beta Cell Hyperfunction

Evidence from studies in both animal models and human subjects indicates that, prior to the onset of diabetes, there is a phase of beta cell hyperfunction characterized by expansion of the mass of beta cells (hyperplasia) and an increase in insulin secretion. These changes are thought to occur as a compensatory response to insulin resistance in skeletal muscle and the liver. Increased delivery of nutrients, including glucose and FFA, is thought to be partially responsible for stimulating the expansion of the beta cell mass and increased insulin secretion. Additionally, insulin itself, insulin-like growth factor 1 (IGF-1), and the gut-derived incretin glucagon-like peptide 1 (GLP-1) have been shown to
enlarge the expression of the PDX1 (pancreatic and duodenal homeobox 1) gene, which is known to increase beta cell survival and stimulate beta cell proliferation. PDX1 gene expression also amplifies insulin secretion in at least 3 important ways: (1) it up-regulates beta cell glucokinase activity, which results in a higher rate of glycolysis within the beta cell; (2) it up-regulates the expression of GLUT-2 glucose transporters; and (3) it up-regulates insulin gene transcription.

A variety of defects contribute to the deterioration of compensatory beta cell hyperfunction and the eventual loss of compensation, heralding the onset of clinically evident diabetes. A by-product of robust oxidation of glucose and FFA is the increased intracellular generation of reactive oxygen species as mitochondrial membrane potential increases. The cellular response to oxidative stress is to increase expression of the UCP-2 (uncoupling protein 2) gene, which reduces mitochondrial membrane potential at the expense of reduced ATP generation. Ultimately, this may interfere with the normal coupling of beta cell glycolysis with cell membrane depolarization and, thus, reduce insulin secretion. Adenosine monophosphate kinase (AMPK) enhances FFA and glucose oxidation and lowers malonyl-CoA activity, normally preventing excessive accumulation of lipid within the beta cell. Increasing intracellular ATP generation by glycolysis and FFA oxidation reduces AMPK activity and allows enhanced malonyl-CoA expression, which in turn allows intracellular lipid accumulation. The further generation of complex lipids can ultimately become cytotoxic and contribute to beta cell apoptosis—a phenomenon that has become known as glucolipotoxicity. Finally, constant demand for high insulin production, borne by the endoplasmic reticulum (ER), results in enhanced folding and unfolding of the ER. In animal models, this phenomenon has been associated with accelerated beta cell apoptosis.6

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**THE TRANSITION TO DIABETES**

**Impaired Insulin Secretion**

In prediabetes or in obesity not complicated by DM, impaired insulin action in muscle, adipose tissue, and the liver is offset by compensatory insulin hypersecretion. Over time, insulin hypersecretion, oxidative stress to the beta cell, and/or glucolipotoxicity may lead to beta cell exhaustion and, ultimately, beta cell failure, as illustrated in Figure 5. As beta cell function declines, glucose tolerance declines as well, resulting in impaired glucose tolerance (IGT) and eventually DM.

Studies of the insulin response to hyperglycemia in patients with type 2 DM and in those with IGT (prediabetes) have shown reduced response to both enteral administration of glucose during the oral glucose tolerance test and to intravenous administration of glucose (first-phase insulin response). Recent evidence confirms that both the first and second phases of insulin secretion are reduced and that secretory defects in both phases (19% reduction in the first phase, 12% in the second phase) are evident before the onset of DM in individuals with a genetic predisposition for type 2 DM.7 Further evidence of the decline in insulin secretion in response to glucose loading comes from a study of Pima Indians (a population with extremely high prevalence of type 2 DM) by Weyer et al.8 These investigators found that the first-phase insulin response was decreased by 27% during the transition from normal glucose tolerance (defined as fasting plasma glucose [FPG] < 100 mg/dL or 2-hr postprandial glucose < 140 mg/dL) to IGT (defined as FPG of 110–126 mg/dL or 2-hr postprandial glucose of 140–199 mg/dL) and was further reduced by 51% during progression from IGT to type 2 DM (defined as FPG > 126 mg/dL or 2-hr postprandial glucose > 200 mg/dL). Nesher et al.9 reported that the degree of peripheral insulin resistance was similar in obese patients with type 2 DM and in lean individuals.
with normal glucose tolerance; however, insulin secretion, as estimated by pancreatic responsiveness scores, was reduced by more than 80% in both lean and obese patients with type 2 DM. Thus, it appears clear that there is a predictable decline in insulin secretion in response to glucose challenge, which parallels the clinical deterioration of glucose homeostasis from normal glucose tolerance to IGT and from IGT to type 2 DM.

**Impaired Proinsulin Cleavage**

As previously noted, insulin is derived from cleavage of the larger proinsulin molecule (synthesized in the ER of the beta cell) into bioactive insulin and physiologically inert C-peptide. In individuals with normal glucose tolerance, the cleavage process is incomplete to the extent that 10% to 15% of secreted insulin is measurable as proinsulin. In contrast, proinsulin constitutes more than 40% of circulating insulin in individuals with type 2 DM. The proinsulin cleavage defect does not appear to be specific for glucose-stimulated insulin secretion, because studies comparing serum insulin and proinsulin concentrations show the same trends in normal subjects as in patients with type 2 DM, even when the nonglucose insulin secretagogues arginine and glucagon are used experimentally. These findings in the aggregate suggest that the postsecretory activation of insulin in type 2 DM is deficient, or that there is insufficient time for the contents of insulin secretory granules to mature properly, in either case resulting in abnormal release of biologically immature proinsulin. The degree of hyperproinsulinemia correlates with the degree of hyperglycemia and beta cell dysfunction.

**Beta Cell Hypofunction and Pancreatic Islet Amyloid in Overt Diabetes**

As previously discussed, increased beta cell mass and insulin hypersecretion gradually yield to receding beta cell mass and a decline in insulin secretion with the emergence of hyperglycemia. Oxidative stress, glucolipotoxicity, unfavorable AMPK/malonyl-CoA signaling, and abnormal folding/unfolding of beta cell ER all may contribute to accelerated beta cell apoptosis and the loss of insulin secretory capacity.

An anatomic finding correlating with type 2 DM in pancreatic islet biopsy specimens is accumulation of amyloid. Islet amyloid polypeptide (also known as amylin) is a 37-amino acid polypeptide originally isolated from amyloid deposits in the pancreatic islets of individuals with type 2 DM. Amylin is stored along with insulin in the secretory granules of beta cells and is co-secreted with insulin, accounting for about 10% of beta cell peptide secretion. Serum amylin concentrations are lower in individuals with IGT and type 2 DM than in those with normal glucose tolerance. Failed secretion of amylin may explain the observed phenomenon of high intracellular amylin concentrations in type 2 DM. There is some evidence that intracellular amylin accumulation impairs beta cell glucose transport, thereby inhibiting insulin secretion. It is therefore possible that amylin accumulation may directly contribute to the pathogenesis of type 2 DM.

Wilding et al identified no effects of amylin on either insulin secretion or insulin action in humans. In rats, the administration of an amylin antagonist in vivo attenuates insulin secretion and thus has a physiologic role in attenuating insulin response to feeding. Amylin may have effects on glucose homeostasis independent of insulin as well. Pramlintide, a synthetic amylin analog, slows gastric emptying (thereby delaying glucose absorption after meals) and induces satiety. It is unclear whether amylin itself plays a causative role in the pathogenesis of type 2 DM or is merely a marker of impaired insulin secretion, and it is not known to what extent the pharmacologic effects of pramlintide are shared in vivo by natural amylin.

**CLINICAL CORRELATES OF DEFECTIVE INSULIN SECRETION**

The anatomic and pathophysiologic changes in insulin secretory capacity are mirrored clinically by the observations of the U.K. Prospective Diabetes Study...
(UKPDS), in which beta cell function was estimated to be 50% of normal at the time of diagnosis of type 2 DM, with progressive decline of function over time.\textsuperscript{18} Worsening hyperglycemia in the UKPDS was evidenced by the finding that only 45% of patients who initially had hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) levels less than 7% maintained that level of glycemic control after 6 years of intensive antihyperglycemic therapy. Insulin resistance did not decline over time, implying that deterioration of beta cell function was responsible for the worsening metabolic profile.\textsuperscript{16}

Although obviously present in the late, overt stages of type 2 DM, insulin secretory defects predate onset of DM, probably by many years. Pimenta et al\textsuperscript{19} showed that both first- and second-phase insulin responses were significantly reduced in Caucasian first-degree relatives of patients with type 2 DM.\textsuperscript{19} These individuals had no demonstrable insulin resistance when compared with age- and sex-matched controls with no family history of DM, which suggests that impaired insulin secretion is due to a genetically determined defect in beta cell function.

**INSULIN RESISTANCE IN TYPE 2 DIABETES**

By definition, insulin resistance is a state wherein the action of insulin on target tissue (skeletal muscle, liver, and adipose tissue) is subnormal, resulting in alteration of normal glucose transport and lipid utilization and storage.\textsuperscript{20} In the setting of tissue insulin resistance, elevated fasting glucose levels are due to increased hepatic gluconeogenesis and glycogenolysis as a result of resistance to the normal restraining influence of insulin on these processes. Postprandial hyperglycemia is primarily attributable to reduced glucose utilization by muscle tissue, related to ineffective insulin-mediated glucose transport.

Much has been published regarding the link between documented insulin resistance and increased risk for developing type 2 DM. Lilioja et al\textsuperscript{21} studied the relative contributions of obesity, beta cell hypo-function, and insulin resistance to the development of type 2 DM in 200 obese Pima Indians with either normal or impaired glucose tolerance. At baseline, subjects were studied with oral glucose tolerance tests, plotting the glycemic and insulin response, and insulin sensitivity was determined by hyperinsulinemic-euglycemic clamp. Insulin resistance was associated with a 27% incidence of DM after 6 years, whereas impaired insulin secretion and normal insulin sensitivity was associated with a 12% incidence of DM, leading the authors to conclude that insulin resistance was the strongest long-term predictor of DM.\textsuperscript{21}

**EFFECTS OF INSULIN RESISTANCE ON GLUCOSE HOMEOSTASIS**

**Hepatic Effects**

In the fasting state, hepatic glucose output (sum of glycogenolysis and gluconeogenesis) averages approximately 2 mg/kg/min in nondiabetic humans; as FPG exceeds 140 mg/dL, this rate increases by about 0.5 mg/kg/min per 50 mg/dL increment in FPG.\textsuperscript{22} Studies in humans have demonstrated that 90% of total hepatic glucose production in type 2 DM is due to gluconeogenesis.\textsuperscript{23,24} A single precise underlying biochemical explanation for accelerated hepatic gluconeogenesis is unknown. Epiphenomena associated with the accelerated gluconeogenesis include hyperglycemia, increased circulating precursor molecules (lactate, alanine, and glycerol), and increased circulating FFA. High levels of circulating FFA are also associated with high levels of intrahepato cellular FFA, which may impede normal glucose phosphorylation and secondary processing by the liver. In the postprandial state, impaired insulin action in the liver is evidenced by hypoactivity of glycogen synthase, resulting in reduced hepatic disposal of a glucose load as compared with the nondiabetic state.\textsuperscript{25} In summary, clinically relevant hepatic correlates of insulin resistance include accelerated gluconeogenesis (the major contributor to fasting hyperglycemia in DM) and decreased postprandial storage of glucose as glycogen (contributing to postprandial hyperglycemia).

**Effects in Skeletal Muscle**

Muscle tissue accounts for up to 85% of glucose uptake by peripheral (nonplanchnic, non-CNS) tissues and is insulin-dependent. The most universal observation in peripheral insulin resistance is reduced GLUT-4–mediated glucose transport\textsuperscript{26,27} in the absence of structural GLUT-4 abnormalities or subnormal total cellular GLUT-4 content.\textsuperscript{28} Rather, the predominant defect appears to be subnormal translocation of intracellular GLUT-4 to the cytoplasmic membrane. Several additional observations may account for impaired insulin signaling in the insulin-resistant state. Subnormal tyrosine kinase activity following insulin–insulin receptor binding has been observed in multiple studies in humans.\textsuperscript{29–31} An obvious effect is impaired activation of phosphoinositide 3-kinase (PIK3), with reduced glyco gen synthesis and reduced inhibition of proteolysis as metabolic consequences.

Once glucose is transported into the myocyte, its fate is dependent on its phosphorylation to glucose-6-phosphate, a conversion dependent on hexokinase-II (HK-II). The activity of HK-II is insulin-dependent, and
several investigators have documented that the activity of HK-II is subnormal in both type 2 DM and IGT. Impaired HK-II–mediated glucose phosphorylation may explain other observed deficiencies in glucose handling by myocytes, including impaired glycogen synthase activity (and resultant reduced glycogen storage) and impaired glucose oxidation. Contributing to impaired glucose oxidation may be a competing process of FFA oxidation attributable to the high levels of circulating FFA characteristic of type 2 DM as well as simple (nondiabetic) human obesity.

**Effects in Adipose Tissue**

The major repository of stored energy is FFA stored as triglyceride in adipose tissue, and the major effect of insulin on adipose tissue is to restrain release of FFA from triglyceride by inhibiting hormone-sensitive lipase. Resistance to this effect of insulin is evident by the universal observation of elevated circulating FFA in type 2 DM, a finding correlated with high intracellular FFA in myocytes and hepatocytes. High levels of intracellular FFA have been strongly associated with impaired insulin action in these target tissues, so impaired insulin action at the level of adipose tissue may represent a common pathway to the overall syndrome of insulin resistance.

**GENETIC INFLUENCES ON INSULIN RESISTANCE**

Insulin exerts its effect by binding to specific cell surface receptors. Insulin receptor mutations have been identified but in the aggregate are rare causes of diabetes. Postreceptor defects presumably affecting one of the intracellular enzymes are thought to play predominate roles in insulin resistance. Polymorphisms in the IRS-2 (insulin receptor substrate 2) gene, calpain-10 gene on chromosome 2A, β-adrenergic receptor, and peroxisome proliferator-activated receptor gamma-2 (PPARγ2) transcription factor have all been implicated as proposed mechanisms in the pathogenesis of insulin resistance. Recent studies also implicate genetic abnormalities involving myocyte mitochondrial function, which may contribute to insulin resistance and later to development of type 2 DM. Petersen et al identified reduced insulin-stimulated glucose uptake by muscle in children of type 2 DM patients as compared with a control group with negative family histories of DM; this finding was correlated with increased intramyocellular lipid, a finding the authors attributed to reduced oxidative phosphorylation.

**CONTRIBUTION OF OBESITY TO INSULIN RESISTANCE**

Intra-abdominal (visceral) obesity is strongly correlated with insulin resistance and is associated with high levels of circulating FFA, resistance to insulin-mediated glucose uptake, and reduced sensitivity of pancreatic beta cells to glucose. The proposed mechanisms linking obesity and insulin resistance are still incompletely understood but include both increased circulating FFA and derangements of circulating peptides released by adipocytes, including tumor necrosis factor-α, interleukin-6, and the adipokines, adiponectin and resistin (Figure 6). Many studies have focused on the role of inflammation as a mediator linking obesity to pathogenesis of type 2 DM. This relationship—and the contribution of adipokines to insulin resistance and impaired insulin secretion—will be explored in part 2 of this review.

**RECOGNIZING INSULIN DEFECTS IN THE CLINIC**

Considering the magnitude of the diabetes epidemic, all clinicians will have almost daily opportunities to either diagnose type 2 DM or to identify and counsel a patient at high risk for the disease. The following case illustrates an opportunity to recognize the physical, familial, and laboratory evidence of insulin resistance and insulin secretory defects and to intervene on behalf of the patient.

**CASE PRESENTATION**

A 35-year-old woman with a history of polycystic ovary syndrome (PCOS) diagnosed at age 18 years is referred to an endocrinology clinic for evaluation. Recent routine blood tests revealed a random serum glucose
level of 180 mg/dL. Aside from PCOS, the patient has no significant past medical history. She has never been pregnant, and her only current medication is a third-generation oral contraceptive pill. Her family history is remarkable for type 2 DM in her father.

Physical examination reveals blood pressure of 120/80 mm Hg, body mass index of 35 kg/m², central obesity, and acanthosis nigricans involving the dorsal neck and axillary skin folds. Other physical examination findings and review of systems are normal.

- How do the historical and physical findings in this patient relate to her abnormal glucose tolerance?

Acanthosis nigricans is a skin lesion highly associated with insulin resistance. Significantly, the patient’s history of PCOS is also associated with insulin resistance and places her at possibly as high as a 40% lifetime risk for developing type 2 DM. The fact that the patient has a first-degree relative with type 2 DM also greatly increases her risk for developing the disease, as does her obesity. While her random blood glucose level (180 mg/dL) is not diagnostic of type 2 DM, it is likely to confer a diagnosis of IGT (prediabetes). Based on all considerations, including her age and multiple risk factors, this patient has a 50% or greater likelihood of developing type 2 DM within 5 years without interventional therapeutic lifestyle changes (diet and regular exercise) or pharmacotherapy (eg, metformin).

Table 2 lists major recognized risk factors for type 2 DM. This patient clearly has several of these risks, as well as cutaneous evidence of impaired insulin action.

- What is the next step in the workup of this patient?

An appropriate next step would be an oral glucose tolerance test to clearly establish whether the patient has type 2 DM or IGT. Although the oral glucose tolerance test is not widely performed for the diagnosis of type 2 DM, the pretest probability of either IGT or type 2 DM in this case is very high, and precise classification may improve the ability to counsel, treat, and expectantly follow the patient over time. One could further consider obtaining a plasma lipid profile to look for dyslipidemia (ie, low level of high-density lipoprotein cholesterol combined with hypertriglyceridemia) and an HbA₁c level, since increased cardiovascular disease risk is conferred by an HbA₁c level greater than 5%.

CASE CONTINUED

The patient undergoes a 75-g oral glucose tolerance test, which reveals an FPG level of 110 mg/dL. Her glucose level 2 hours after the administration of 75-g oral glucose is 120 mg/dL. Based on these findings, the patient is diagnosed with IGT. She is advised that she is on her way to developing type 2 DM and would benefit from starting therapy with a drug that can help improve the action of insulin. Because she is obese, metformin therapy is recommended. However, the patient ultimately chooses not to start the medication.

One year later, the patient is referred back to the clinic with complaints of polyuria, polydipsia, and blurred vision. A random plasma glucose measurement is 250 mg/dL. A urine dipstick test is negative for ketones but positive for 3+ glucose. Additionally, the patient has gained 15 lb (6.82 kg) in the last year.

- What are the best management options for this patient at this time?

Based on the presence of classic symptoms of hyperglycemia (polyuria, polydipsia, blurred vision) and the confirmation of a random plasma glucose level greater than 200 mg/dL, the diagnosis of type 2 DM is now definite and unambiguous (Figure 7). In addition to renewed efforts to implement a healthy diet and exercise plan designed to foster weight reduction, one could consider various pharmacotherapy options, which could include insulin, metformin, a TZD, and/or an incretin. Of the available options, metformin is rational because its primary action is to impede gluconeogenesis, and it is frequently associated with a small but significant net weight loss after 12 months of treatment. Reduction
in weight usually improves insulin resistance, which may in turn reduce glucolipotoxicity and improve insulin secretory function. TZDs improve insulin action through their agonism of PPARγ, which is associated with improved GLUT-4 synthesis and activity. Incretins may promote satiety and are usually associated with durable weight loss, although the long-term effect on glucose homeostasis remains to be established.

**CONCLUSION**

The pathogenesis of type 2 DM involves twin derangements of impaired insulin action (insulin resistance) and impaired (and progressive) insulin hyposecretion relative to the observed degree of hyperglycemia. In many cases of genetically susceptible prediabetic individuals, physical evidence of abnormal insulin action may predate overt DM by many years. Tell-tale evidence of insulin resistance includes increased FFA accumulation in myocytes and reduced GLUT-4 activity of myocytes in response to insulin receptor binding. As postprandial hyperglycemia increases over time, defective insulin secretion from pancreatic beta cells becomes evident and culminates in the most obvious expression of DM—the onset of fasting hyperglycemia. The implication of fasting hyperglycemia is that the usual restraining effect of insulin on hepatic gluconeogenesis has been lost, perhaps on the basis of excessive FFA and/or non–insulin-mediated glucose accumulation in hepatocytes.

Historically, type 2 DM has displayed a natural history of progressive failure of normal glucoregulatory homeostatic mechanisms and resistance to increasingly complex pharmacotherapy targeting multiple defects. A modern and evolving strategy of care is aimed at delaying or even preventing the onset of DM in at-risk individuals by aggressively intervening with lifestyle changes known to improve insulin action and, possibly, through proven drug therapy. Preventing DM clearly offers the greatest promise for minimizing the devastating complications of this raging disease.

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