The epidemic of type 2 diabetes mellitus is increasing in most nations. This illness is a major cause of cardiovascular disease, stroke, blindness, renal failure, and amputations. Because available interventions have failed to show durability, new modes of therapy need to be directed at the underlying causes of abnormal glucose metabolism. The development of such modes of therapy will require an improved understanding of how the β-cell mass compensates for changes in insulin resistance and why β cells lose the capacity to secrete insulin. In addition, new therapeutic modalities need to address α-cell dysregulation, because the inability to suppress glucagon production results in ongoing elevated levels of hepatic glucose.

Diabetes mellitus is a worldwide epidemic. Global projections suggest that most nations will have a doubling of the incidence of diabetes mellitus within 20 years.1 Wild et al1 estimated, based on data from the World Health Organization and United Nations, that there were approximately 171 million people with type 2 diabetes mellitus (T2DM) in 2000, and that this number would grow to 366 million by 2030. This epidemic involves all parts of the globe—with India, China, and the Middle East impacted more than Europe, Africa, and North and South America.1

The most important risk factor for the development of T2DM is obesity. Although the detailed mechanisms for the genesis of T2DM are not known, the association with obesity is strong. Colditz et al2 estimated that a body mass index...
Diabetes mellitus is also heterogeneous with regard to ethnic groups—and even to expression within families. Diabetes mellitus is not inherited in a simple Mendelian manner; there is no unique set of genes that determines the development of T2DM. Rather, many genes have been identified as T2DM risk factors. Scadet al recently presented data on a genome-wide search that revealed four previously unknown genes that confer T2DM risk. Additional T2DM-related genes are expected to be found. However, to reiterate, genes may confer risk for T2DM, but the major factor determining the expression of T2DM is lifestyle—particularly overeating and physical inactivity.

Pancreatic β-Cell Dysfunction

Precisely why does T2DM develop in some individuals as weight and insulin resistance increase? Part of the answer involves dysregulation of the α and β islet cells of the pancreas.

An early event in the α-cell dysfunction is the failure to secrete adequate insulin at the proper time. Weyer et al demonstrated this secretory failure when comparing people with normal glucose tolerance (NGT) with those with impaired glucose tolerance (IGT) and T2DM. The experimental design measured the first-phase insulin response, also known as the acute insulin response, which is a small but rapid spike of insulin secretion that occurs within minutes after a glucose challenge.

In the real world, a first-phase response is not actually seen, but rather a peak of insulin is detected about 30 minutes after eating. However, the fine details of this initial insulin response can be delineated using a technique called the hyperglycemic glucose clamp. If a person is given a sustained intravenous glucose challenge, a short burst of insulin can be measured within about 10 minutes postchallenge. This early insulin production then declines to baseline levels and is soon followed by a second phase of insulin secretion that is sustained during hyperglycemia.

When the first-phase insulin response is studied in a population, a clearer picture emerges about the maintenance of normal blood glucose and the progression from NGT to IGT to T2DM. Figure 1 illustrates how people with NGT can exhibit a wide range of responses to an intravenous glucose challenge. Some individuals handle the glucose challenge well, maintaining their glucose control with only a small first-phase insulin response. These people are insulin-sensitive (i.e., they have low insulin resistance). Other individuals with NGT are less insulin-sensitive and generate a larger first-phase insulin response to effectively manage the glucose challenge. In both cases, however, insulin secretion is sufficient to overcome the degree of insulin resistance, and glycemic control is maintained within a normal range.

Defects in an individual’s insulin secretion are often first detected when the individual has IGT. People with IGT have normal fasting glucose levels, but they “drop off the curve” when given an intravenous glucose challenge. As seen in Figure 2, people who have IGT produce a first-phase insulin response, but it is suboptimal compared with the response in those who have NGT. As a result, the glucose challenge causes the blood glucose level of people with IGT to rise above the normal range. Compared with individuals who have NGT, the first-phase insulin secretion in people with IGT is decreased about 25%. Individuals with T2DM have essentially no acute insulin response to a glucose challenge.

The first-phase insulin response is clinically relevant. Its loss contributes to about 50% of the postprandial hyperglycemic excursion. Another way to view the importance of the first-phase insulin response is to consider the fact that individuals with IGT or T2DM have the following two problems in controlling their glucose levels:

■ They have insufficient insulin to downregulate ongoing glucose production from the liver.
■ They have insufficient insulin to deal with glucose derived from meals.

Thus, it is not surprising that postprandial glucose levels can increase to between 200 mg/dL and 400 mg/dL in individuals with T2DM. Individuals
with normal glucose metabolism have an intact first-phase insulin response that turns off hepatic glucose production. In these individuals, sufficient insulin is secreted at the proper times to dispose of mealtime glucose loads.

Degeneration of the first-phase insulin response is a marker of β-cell failure and portends conditions that are likely to deteriorate from IGT to T2DM. However, the path from IGT to T2DM is not inevitable. Physiologic mechanisms exist for compensation when insulin resistance changes. For example, when people with NGT gain weight, they secrete more insulin to maintain euglycemia. When they lose weight, they secrete less insulin to maintain euglycemia. By contrast, when people with IGT gain weight, they secrete more insulin to maintain euglycemia. When they lose weight, they secrete less insulin to maintain euglycemia. Thus, individuals with IGT exhibit an insulin secretory defect. When these individuals lose weight, their insulin secretion improves. Five clinical trials have shown that it is possible to prevent 30% to 50% of the T2DM cases in individuals with IGT by using weight loss and exercise.

In addition to the defects in insulin secretion that occur in individuals with IGT and T2DM, the β-cell mass in the pancreas decreases as hyperglycemia develops. Normally, the β-cell mass is dynamic, changing depending on the individual’s metabolic demands. The β-cell mass can expand when β cells replicate, undergo hypertrophy, or arise by differentiation of precursor cells. Each of these three paths can lead to increased insulin capacity. The β-cell mass can decrease by both apoptosis and necrosis. Individuals without T2DM establish equilibrium between β-cell recruitment and β-cell death, so that normal glucose metabolism is preserved.

In individuals with T2DM, β-cell loss predominates so that over time, there is an absolute loss of β cells. Butler et al used autopsy data to document the loss of β cells in people with abnormal glucose metabolism. People with IGT and T2DM had approximately 40% and 60% less β-cell mass, respectively, compared with counterparts with normal glucose tolerance.

It is unknown why β cells are lost in individuals with T2DM, but several conjectures exist. For example, elevated glucose and free fatty acids (i.e., glucolipotoxicity) may induce apoptosis. Perhaps oxidative stress as a consequence of glucolipotoxicity induces β cells to enter an apoptotic pathway of programmed cell death. Whatever the actual mechanism of β-cell loss, the result is that a relative insulin deficiency—and eventually an absolute insulin deficiency—occurs.

Pancreatic α-Cell Dysfunction
Defects in insulin secretion and loss of β cells make up only part of the explanation of why T2DM develops. There are other major pathways that play important roles in glucose metabolism. These include counter-regulation by glucagon and modulation of insulin and glucagon secretion by intestinal hormones called incretins. Counter-regulation by glucagon is discussed in the present report. A report by Jeffrey S. Freeman, DO, in this JAOA supplement issue (2007;107[suppl 3]:S6-S9) describes...
the pathophysiologic role of incretins in the regulation of insulin secretion and glucagon suppression.

Counter-regulation is the mechanism in which hypoglycemia is prevented. Just as it is necessary to use glucose for energy production, it is equally important to be able to produce glucose when energy stores decrease. In normal physiologic mechanisms, when blood glucose increases, insulin is upregulated and glucagon production by the α cells of the pancreas is suppressed. Conversely, when blood glucose decreases, β cells secrete less insulin, glucagon secretion is upregulated, and hepatic glycogen stores are converted into glucose. Glucagon is the most important of the counter-regulatory hormones.

Epinephrine plays a lesser role in counter-regulation, while growth hormones and cortisol are not relevant in the acute regulation of glucose. The magnitude of the glucagon effect on hepatic glucose output was demonstrated by Liljenquist et al., who found that administration of somatostatin inhibited glucagon secretion and resulted in a 75% decrease in hepatic glucose production.

More than three decades ago, Unger described the relationships between glucose, insulin, and glucagon in individuals with NGT and T2DM. Muller et al. reported similar data. Figure 3 shows both the normal response and the T2DM response to a carbohydrate challenge (ie, meal). In the Unger et al. experiments, fasting glucose levels increased from approximately 80 mg/dL to 130 mg/dL at 1 hour after the carbohydrate challenge in individuals with NGT. There was also a rise in the plasma insulin level that paralleled the change in glucose concentration. Glucagon secretion in individuals with NGT abruptly decreased as glucose and insulin levels increased. Glucagon secretion remained suppressed until the glucose returned to fasting levels and insulin returned to basal levels.

Unger found very different relationships in people with T2DM. The fasting glucose level in these individuals was elevated, as expected in T2DM, and it increased to about 300 mg/dL after the carbohydrate challenge. Subsequently, there was a blunted and delayed insulin response, with glucagon regulation showing the following three abnormalities:

- The baseline level for glucagon was elevated in individuals with T2DM compared with that in the nondiabetic counterpart.
- Glucagon secretion increased as glucose was absorbed from the challenge meal.
- Glucagon remained elevated for about 2 hours and then slowly returned to the abnormal baseline level.

Mitakou et al. found that people with IGT showed an intermediate level of glucagon dysregulation. After a glucose challenge, these individuals had a delayed insulin response, and postprandial hyperglycemia occurred. The baseline glucagon levels in individuals with IGT were similar to those found in individuals with NGT, but dysregulation was evident in that glucagon was only 50% suppressed, compared with glucagon levels in healthy control subjects. Thus, the progression from NGT to IGT to T2DM is also marked by the progressive loss of the capacity to suppress glucagon.

Comment

Many physiologic abnormalities can lead to T2DM. For most people, the path to T2DM begins with weight gain. DeFronzo et al. proposed that hyperlipidemia associated with obesity contributes to insulin resistance. The mechanisms related to this process involve increases in free fatty acids, which affect muscle tissue, the liver, and the pancreas. Muscle tissue in individuals with T2DM uses fatty acids, rather than glucose, as an energy source, which leads to decreased glucose disposal and subsequent hyperglycemia. The liver oxidizes fatty acids, signaling increased gluconeogenesis. The pancreas in an individual with T2DM secretes less insulin because fatty acids downregulate the β-cell response to glucose.

Thus, part of insulin resistance involves less effective glucose disposal by peripheral tissues, increased hepatic glucose production, and less efficient insulin secretion. If an individual is able to compensate for these abnormalities by increasing insulin production, normal blood glucose levels can be maintained for many years despite high levels of insulin resistance. However, those individuals with genetic risk factors for T2DM may be unable to increase β-cell function to match their degree of insulin resistance. The first sign of β-cell failure is loss of the first-phase insulin response and the development of IGT.

![Figure 3](image-url)
tantly, there is the loss of about 50% of the capacity to suppress glucagon, which further exacerbates hyperglycemia.12

Regulation of glucagon is poorly understood, but it appears that pancreatic α cells lose their responsiveness to hyperglycemia and continue to secrete glucagon.30 In addition, the α cells become less sensitive to the inhibitory effects of insulin on glucagon secretion.30 At this stage, T2DM can still be prevented or delayed in many people if insulin resistance is decreased.

The most effective known intervention to decrease insulin resistance consists of exercise and weight loss. Most of the studies show that diet and exercise can prevent twice as many cases of diabetes as oral agents.16-20 If insulin resistance and β-cell loss continue, however, T2DM will develop, characterized by hyperglycemia, hyperglucagonemia, insulin deficiency, and dysregulation of incretins—including glucagon-like peptide 1 (GLP-1) and glucagon-dependent insulinotropic peptide (GIP).

The most promising research on reversing T2DM focuses on reconstitution of the β-cell mass. Use of immunologic modifiers of inflammation, including monoclonal antibodies directed against T cells and cytokines, are aimed at decreasing β-cell loss. Biologics, such as GLP-1 analogs, gastrin, and epidermal cell growth factor, focus on induction of β-cell neogenesis.

Such approaches may be productive in consideration of the following fact: the main difference between IGT and T2DM is the further decline in the β-cell mass from approximately 40% in IGT to 60% in T2DM.22 Thus, it may not be necessary to restore the β-cell mass to a pristinem state. Rather, perhaps all that is required is the ability to expand the number of β cells by 20%.

References