Pathophysiology of Type 2 Diabetes: Targeting Islet Cell Dysfunction

Craig W. Spellman, DO, PhD

Type 2 diabetes mellitus (T2DM) continues to be a major health problem worldwide. It is well known that T2DM is a metabolic disorder characterized by hyperglycemia, which arises from insufficient pancreatic insulin secretion, insulin resistance in peripheral tissues, and inadequate suppression of glucagon production. This suppression results in inadequate uptake, storage, and disposal of ingested glucose accompanied by elevated hepatic production of glucose and profound hyperglycemia. Notably, these pathophysiologic processes can progress to a clinically significant degree even in patients with impaired glucose tolerance. As researchers begin to unravel the genetic basis of T2DM, the gradual accumulation of genetic polymorphisms in multiple genes—rather than the mutation of a single “diabetes gene”—appears to be the driving force behind the increase in T2DM risk. Emergent therapies for the management of T2DM include incretin-based agents, which can effectively target two key processes in T2DM by augmenting insulin secretion and inhibiting glucagon production.

The epidemic of type 2 diabetes mellitus (T2DM) in most developed nations continues unabated. Projections based on World Health Organization and United Nations population data indicate a doubling of the incidence of T2DM by the year 2030.1 As awareness of this disease evolves, so does the development and implementation of newer, more efficient, and targeted therapies for the management of T2DM.

The metabolic manifestations of T2DM include hyperglycemia, which results from resistance to insulin actions in peripheral tissues as well as inadequate secretion of insulin,2 and an impaired suppression of glucagon secretion in response to ingested glucose. Thus, T2DM involves at least two primary pathogenic mechanisms: (1) a progressive decline in pancreatic islet cell function resulting in reduced insulin secretion and inadequate suppression of glucagon secretion,3,4 and (2) peripheral insulin resistance resulting in a decrease in the metabolic responses to insulin.2,3,5

Endocrine Cells of the Pancreas

Located in the islets of Langerhans, endocrine cells of the pancreas are comprised primarily of two types of cells—α and β cells. Large interspecies variations in islet cell architecture exist in terms of cell quantity and location. In mice, β cells are clustered in the core of the islet and α cells are localized to the periphery of the islet. In humans, α and β cells are found scattered throughout the islet along blood vessels in association with microcirculation.

The β cells comprise approximately 60% of the endocrine mass of the pancreas6 and produce both insulin and amylin, the former of which is released in response to elevation in plasma glucose levels. The α cells, which comprise about 30% of the endocrine mass of the pancreas, secrete glucagon in response to decreases in plasma glucose levels.6 The pathogenic mechanisms in T2DM involve not only insulin, but also glucagon, and it is the interplay between these two processes that is a key component in...
the understanding of the pathophysiology of T2DM.

Response to Glucose

The metabolic response to ingested carbohydrate is markedly different in individuals with normal glucose tolerance compared to those with T2DM. Individuals with normal glucose metabolism have a typical insulin, glucose, and glucagon profile in plasma in response to the ingestion of a carbohydrate meal (Figure 1). After ingestion, there is a predictable increase in plasma glucose levels as well as a robust insulin response to dispose of the ingested glucose load; in contrast, however, glucagon secretion is discontinued and plasma levels of this mediator decrease (Figure 1).

This interaction represents the ideal response of both pancreatic α- and β-cell types. It allows plasma glucose to remain within a very narrow homeostatic range despite the wide variation in food intake that occurs with the transition from the fasting to the fed state. Both the increase in insulin secretion and the decrease in glucagon levels are required to promote optimal storage and disposal of glucose. Insulin and glucagon thus represent a key set of counterregulatory hormones involved in the metabolic response to glucose.

Pathogenic Mechanisms

One key reason underlying the profound postprandial hyperglycemia observed in patients with T2DM is a decrease in the peripheral uptake of glucose. In response to increasing insulin levels in normal individuals as well as those with T2DM, peripheral uptake of glucose occurs; however, the efficiency of uptake in patients with T2DM is markedly reduced. A study evaluating the rate of total body glucose disposal as a function of increasing insulin concentrations showed the rate of glucose uptake was reduced by about 30% in patients with T2DM, compared with control patients, at the two highest concentrations of insulin (P < .01). The same study also demonstrated that basal hepatic glucose production (HGP) was significantly greater in patients with T2DM than in control subjects (mean [SD], 83 [4] vs 71 [2] mg/mg²/min; P < .01). Fasting plasma glucose (FPG) was also significantly correlated with basal HGP (r = 0.82; P < .01). These findings suggest that the level of insulin production achieved in a patient with T2DM is insufficient to control hyperglycemia.

Patients with T2DM also have a reduced uptake of glucose into cells, less efficient shunting of glucose into key metabolic pathways such as the tricarboxylic acid cycle, and less storage of glycogen. In one series of glucose clamping experiments, an impaired rate of glucose disposal was shown in patients with T2DM as well as in those with IGT. Mean rates of glucose disposal in both groups were significantly less compared with control subjects (P < .01). Results from these studies also suggested a spectrum of defects in patients with varying degrees of glucose intolerance, including reduced insulin receptor expression and defects in the postreceptor actions of insulin. Thus, patients with T2DM may have impairment in glucose uptake mechanisms and in the utilization and disposal of excess glucose once inside the cell. Glucose stays elevated in the periphery because insulin-stimulated glucose uptake—as well as insulin-stimulated glycogen synthesis—are reduced.

A key reason for postprandial glucose elevation in T2DM relates to the blunted glucose-stimulated production of insulin. While many potential mechanisms may account for this phenomenon, the reduction of pancreatic β-cell mass in patients with T2DM is worth noting. Results from autopsy studies of obese individuals characterized as having either normal glucose tolerance (NGT, n=31), impaired fasting glucose (IFG, n=19), or T2DM (n=41) showed that, with progression from NGT to IFG to T2DM, β-
cell masses progressively decrease (Figure 3). Patients with IFG had a 40% decrease in relative β-cell volume \((P < .05)\), whereas those with T2DM had a 63% decrease, compared to the NGT group \((P < .01)\). The authors concluded that obese and lean patients with T2DM experience a loss of β-cell volume, and, presumptively, β-cell mass, compared to their nondiabetic weight- andagematched cohorts. The mechanism of this loss was attributed to an increase in β-cell apoptosis when compared to a change in the rate of new islet formation.

The progression from NGT to IGT in this study is noteworthy for physicians because patients with glucose levels of 102 to 111 mg/dL would ordinarily not arouse much concern, yet these patients would have already lost about 40% of their β-cell mass. By the time T2DM was diagnosed, the loss would be at least 60%. Thus, one reason for low insulin and, consequently, hyperglycemia, in patients with T2DM is the progressive loss of pancreatic β cells.

Similar results have been reported in other clinical trials, in which not only has pancreatic islet cell mass decreased in patients with T2DM, but the remaining islets do not function properly. Islets from the pancreas of cadaveric T2DM \((n=14)\) and normal cadaveric donors \((n=14)\) were isolated and matched for age, body mass index, and cold ischemia time. A significant difference in islet cell mass between patients with T2DM and normal donors \((256,260 \text{ vs } 597,569 \text{ islet equivalents, respectively; } P < .001)\) was observed, which showed significantly reduced islet cell mass in patients with T2DM. Moreover, patients with T2DM had poorer islet function compared to controls. The threshold for glucose-stimulated insulin release (GSIR) was 7 and 12 mmol/L in normal vs diabetic islets, and the GSIR peak rate of normal subjects was twice that of patients with T2DM, demonstrating a poorer sensitivity to glucose. These results suggest a loss of islet mass and an apparent decline in islet cell function in patients with T2DM.

**Genetics**

The advent of modern molecular biological techniques has been an invaluable resource for the genetic study of various diseases, including T2DM. Researchers can now identify and characterize many of the specific genes associated with the disease process in T2DM. Using reverse genetics, researchers can ultimately identify the functional deficits involved and intervene therapeutically. The development of low-cost, single-nucleotide polymorphism (SNP) arrays has allowed for an evaluation of the potential association of particular SNPs with T2DM on a genome-wide scale. As a result of these efforts, researchers have now identified at least 27 confirmed or potential genes involved in patient susceptibility to T2DM. Figure 4 summarizes the genes confirmed to be involved in T2DM.

Given the significance of the mech-
anisms behind the functioning of β cells, it is interesting to note that many of these genes are involved in β-cell function and physiology (Figure 4). Although many other factors may play a substantial role, these findings are consistent with the global notion that T2DM is essentially a β-cell disease, and β-cell dysfunction in T2DM may be determined largely by genetics.

An important concept to remember when considering the genetics of T2DM is that it is not the presence of a specific gene that causes T2DM per se, but rather the presence of DNA sequence variants that appear to be associated with differences in metabolic functions in patients with T2DM. Many genes related to diabetes factor into the risk of developing T2DM. Moreover, each gene, in and of itself, contributes a small portion of this risk. Thus, the presence of greater numbers of diabetes-associated SNP variants increases the risk of developing T2DM.

One of the strongest associations with T2DM involves the gene that encodes transcription factor 7-like 2 (TCF7L2), which confers an overall allelic risk for T2DM of more than 1.4 per risk allele. This gene encodes a transcription factor that controls the expression of multiple downstream effector genes involved in a highly conserved signaling pathway, and a small variation in the activity or rate of activity of this gene can have a clinically significant metabolic impact. Studies suggest that the product of the TCF7L2 gene plays an important role in β-cell survival and proliferation as well as in the insulin secretory response of these cells.

Insulin resistance relates, in part, to the inability to transport glucose into cells. When glucose enters a cell, the metabolism is altered and glucose is not properly stored or utilized. An analysis of these genes and their variant forms makes it possible to understand these processes at cellular and molecular levels. For example, the TCF7L2 gene encodes a pore-forming subunit of an adenosine triphosphate (ATP)-sensitive potassium channel that is present on β cells. This channel links the detection of glucose (and its conversion to ATP) to membrane depolarization on the β cell, which leads ultimately to the exocytosis of insulin granules.

A variant of the KCNJ11 gene that has been identified and confirmed to have an impact in T2DM encodes a slightly altered protein product that causes the channel to remain open, thereby impairing the proper response to ATP. The net result is an impairment of β cells’ response to glucose and its ability to secrete insulin appropriately.

In the case of TCF7L2, variants in this gene may impact the expression of the genes encoding proprotein convertase types 1 and 2, which are involved in the conversion of proinsulin to insulin. These two examples demonstrate how small variations in genes can lead to some of the key metabolic defects associated with T2DM. In the case of KCNJ11, an altered protein subunit of a β-cell channel ultimately leads to impairment of β-cell response in insulin secretion, whereas in the case of TCF7L2, altered activity of a highly conserved transcription factor leads to impaired processing of insulin.

The key point is that small variations in each of these genes contribute to an alteration in the function of their respective protein products. These influences on protein function, in turn, may have effects on parameters, including insulin secretion, release, and processing, thereby increasing an individual’s overall risk of developing T2DM. Further study of these gene products, and the identification of other genes associated with T2DM, thus provide a basis for further understanding of the processes that contribute to this disease and the development of new therapies.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Risk Allele Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS9</td>
<td>Unknown</td>
</tr>
<tr>
<td>CAPN10†</td>
<td>Decreased glucose-stimulated insulin secretion; decreased proinsulin conversion; decreased whole-body insulin sensitivity</td>
</tr>
<tr>
<td>CDC123/CAMK1D†</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>CDKAL1†</td>
<td>Decreased glucose-stimulated insulin secretion; decreased proinsulin conversion</td>
</tr>
<tr>
<td>CDKN2A/B†</td>
<td>Decreased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>ENPP1†</td>
<td>Decreased whole-body insulin sensitivity; decreased insulin secretion</td>
</tr>
<tr>
<td>FTO</td>
<td>Increased overall fat mass; increased energy intake; decreased cerebrocortical insulin sensitivity</td>
</tr>
<tr>
<td>HHEX†</td>
<td>Decreased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>HNF1B (TCF2)</td>
<td>Unknown</td>
</tr>
<tr>
<td>IGF2BP2†</td>
<td>Decreased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>JAZF1†</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>KCNJ1†</td>
<td>Decreased insulin secretion; decreased glucose-dependent suppression of glucagon secretion</td>
</tr>
<tr>
<td>KNCQ1†</td>
<td>Decreased insulin secretion; decreased incretin secretion</td>
</tr>
<tr>
<td>MTNR1B†</td>
<td>Decreased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>NOTCH2</td>
<td>Unknown</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Decreased whole-body insulin sensitivity; decreased adipose tissue sensitivity; decreased insulin clearance</td>
</tr>
<tr>
<td>SLC30A8†</td>
<td>Decreased glucose-stimulated insulin secretion; decreased proinsulin conversion</td>
</tr>
<tr>
<td>TCF7L2†</td>
<td>Decreased incretin-stimulated insulin secretion; decreased proinsulin conversion; decreased whole-body insulin sensitivity; decreased hepatic insulin sensitivity</td>
</tr>
<tr>
<td>THADA</td>
<td>Unknown</td>
</tr>
<tr>
<td>TSPAN8/LGR5†</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>WFS1†</td>
<td>Decreased incretin-stimulated insulin secretion</td>
</tr>
</tbody>
</table>

Hepatic Glucose Production and the Incretin Effect

The key metabolic defects associated with T2DM are reduced insulin production and secretion, increased insulin resistance, and continued production of glucagon. Another key component of hyperglycemia associated with T2DM is the basal rate of glucose production by the liver; compared to a person with normal glucose metabolism, basal HGP in patients with T2DM is markedly elevated. Thus, in addition to having less efficient postprandial glucose transport and metabolism, individuals with T2DM also have elevated production of glucose by their liver, resulting in markedly elevated postprandial plasma glucose levels.

The possible mechanisms of elevated basal HGP lies in the process by which hepatic gluconeogenesis is switched off. In particular, a deficiency in glucagon production causes a profound and sustained reduction in HGP. In one study, healthy non-obese men were treated with an infusion of somatostatin to suppress endogenous plasma insulin and glucagon levels. Results demonstrated that glucagon levels were reduced by more than 50% in these subjects, and, simultaneously, HGP was reduced by 75% and remained suppressed throughout the study, as assessed by net splanchnic glucose production. These results highlight the importance of reducing glucagon levels in the suppression of HGP in patients with T2DM as well as the important role of glucagon in sustaining HGP in normal individuals. In T2DM, postprandial glucagon secretion is not suppressed as it is in normal individuals, and in fact, may even increase (Figure 2).

The net result of elevated glucagon levels is that the liver will continue to produce glucose, regardless of whether it is needed or not. However, the impaired glucagon suppression observed in patients with T2DM is also seen to some degree in patients with IGT; up to half of glucagon suppression is lost in patients whose glucose is 104 to 111 mg/dL.

In a study investigating plasma insulin and glucagon response after ingestion of an oral glucose load, both non-obese and obese patients with IGT were compared to age- and weight-matched normal patients. The results showed mean (SD) FPG levels to be significantly higher in patients with IGT (non-obese: normal, 5.2 [0.6] mmol/L; IGT, 6.2 [0.6] mmol/L; and obese: normal, 5.2 [0.5] mmol/L; IGT, 6.1 [0.5] mmol/L; \( P < .02 \)). Moreover, whereas arterial glucagon decreased significantly (\( P < .01 \)) within 30 minutes of glucose ingestion in normal patients, those with IGT did not experience this decrease until 60 minutes, and the nadir values were significantly higher than in the normal patients. These findings suggest a significant impairment of glucagon suppression after glucose ingestion even in patients with IGT. These findings also highlight the significance of IGT as a clinical condition. Therefore, initiating more aggressive treatment for patients with IGT should be considered in the future.

The importance of both insulin and glucagon in the pathogenesis of T2DM has supported the development of new types of treatment—namely, incretin-based therapies. The existence of incretins was postulated in the early 1900s when investigators first observed a fundamental difference in the plasma insulin response when equimolar amounts of glucose were administered by the oral or intravenous (IV) route (Figure 5). A later study confirmed the presence of a significantly greater insulin response to orally administered glucose compared to the same amount of IV-administered glucose. The term incretin effect refers to the difference between these two plasma insulin profiles. This differential effect of oral vs IV glucose suggested the existence of substances in the gut that mediate this response and led to the discovery of incretins. Moreover, a key role for these incretins in the pathogenesis of diabetes is suggested by the finding that the incretin effect is substantially blunted in patients with T2DM (Figure 5).

Two major incretins—glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide—are peptide hormones secreted by cells in the gut that stimulate insulin secretion, and, in the case of GLP-1, inhibit glucagon secretion. The dual action of GLP-1 in both stimulating insulin secretion as well as inhibiting glucagon secretion highlights its potential benefit in the treatment of the two key metabolic abnormalities associated with T2DM. Also, the exogenous administration of GLP-1 to patients with poorly controlled T2DM has been shown to normalize plasma glucose levels and reduce glucagon secre-
tion.23 Presently, there are two types of therapies directed at enhancing incretin action for the treatment of T2DM: dipeptidyl peptidase-4 inhibitor agents and GLP-1 agonists. Together, these form the basis for a new paradigm in T2DM therapy, which has the potential to slow the progression of islet cell dysfunction in patients with T2DM.23

**Conclusion**

The pathophysiology of T2DM is multifaceted and includes insulin secretion from pancreatic islet cells, insulin resistance in peripheral tissues, and inadequate suppression of glucagon production. These processes result in inadequate uptake, storage, and disposal of ingested glucose accompanied by elevated hepatic production of glucose and hyperglycemia. Loss of β-cell mass in the pancreatic islets can progress to a clinically significant degree even in patients with IGT, such that at the time of diagnosis of T2DM, a significant number of cells may already be lost.

Multiple genes have been identified that are involved in the development of T2DM, increasing our understanding of the pathophysiology of T2DM and offering potential new treatment options. Newer therapies for the management of T2DM include incretin-based agents, which act by targeting many of the key pathophysiologic processes in T2DM, including enhancing insulin secretion and inhibiting glucagon production.

**References**


