

## Examining the Mechanisms of Glucose Regulation

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### Abstract

The prevalence of diabetes mellitus (DM) increased by 49% between 1990 and 2000, reaching nearly epidemic proportions. In 2010, DM (type 1 or 2) was estimated to affect nearly 30% (10.9 million) of people 65 years and older and 215,000 of those younger than 20 years. Macrovascular and microvascular complications can occur; DM is a major cause of heart disease and stroke, and is the seventh leading cause of death in the United States. Based on 2007 data, the economic impact of DM is considerable, with total costs, direct medical costs, and indirect costs estimated at \$174 billion, \$116 billion, and \$58 billion, respectively. Normal glucose regulation is maintained by an intricate interaction between pancreatic  $\beta$ -cells (insulin/amylin), pancreatic  $\alpha$ -cells (glucagon), and associated organs (eg, intestines, liver, skeletal muscle, adipose tissue). Newly elucidated mechanisms include the involvement of the kidneys in glucose regulation, as well as central glucose regulation by the brain. The central defects in type 2 diabetes mellitus (T2DM) are decreased insulin secretion, glucoregulatory hormone deficiency/resistance, and insulin resistance, resulting in abnormal glucose homeostasis. This article provides an extensive review of mechanisms involved in physiologic blood glucose regulation and imbalances in glucose homeostasis.

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For author information and disclosures, see end of text.

Despite vigorous research aimed at combating type 2 diabetes mellitus (T2DM) and the availability of numerous medications, this disease continues to affect people of all ages, and the prevalence of diabetes mellitus (DM) has reached epidemic proportions. Currently, an estimated 25.8 million individuals are affected by DM (both type 1 and type 2).<sup>1</sup> From 1990 to 2000, the prevalence of DM increased by 49%, a rise that appears linked to the increasing rate of obesity.<sup>1</sup> In 2010, type 1 or 2 DM was estimated to affect nearly 30% (10.9 million) of people 65 years and older, and 215,000 of those younger than 20 years. Approximately 1.9 million people older than 20 years were newly diagnosed with DM, and up to 45% of newly diagnosed children had T2DM, with the majority being overweight or obese.<sup>2</sup> In 2005 to 2008, based on fasting glucose or glycated hemoglobin (A1C) levels, 35% of adults older than 20 years, and 50% of those older than 65 years, had prediabetes. Applying this percentage to the entire US population in 2010 yields an estimated 79 million American adults older than 20 years with prediabetes.<sup>1</sup>

DM is a major cause of heart disease and stroke, and is the seventh leading cause of death in the United States. DM is also the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults.<sup>1</sup> With respect to complications, the rising incidence of T2DM in children is particularly alarming, because as people develop the disease at a younger age, they may experience significant morbidity and potential mortality in their fourth decade of life.<sup>2</sup> The aging of the population is also expected to drive a substantial increase in the incidence of DM and associated complications, particularly since research has found that elderly people with newly diagnosed DM experience much higher rates of complications in the years after diagnosis than do their peers without DM.<sup>2</sup>

Based on 2007 data, the economic impact of DM is considerable, with total costs, direct medical costs, and indirect costs (eg, disability, work loss, premature mortality) estimated at \$174 billion, \$116 billion, and \$58 billion, respectively.<sup>1</sup> Medical costs attributed to DM include \$27 billion for direct care of the disease, \$58 billion for treatment of DM-related chronic complications (Figure 1), and \$31 billion in excess general medical costs.<sup>2</sup> The

largest components of medical expenditures attributed to DM are hospital inpatient care (50% of total cost), medication and supplies for DM (12%), retail prescriptions for DM complications (11%), and physician office visits (9%). People with diagnosed DM incur average expenditures of \$11,744 per year, of which \$6649 is attributed directly to the disease.<sup>2</sup> After adjusting for population age and sex differences, average medical expenditures among people diagnosed with DM are estimated to be 2.3 times higher than what expenditures would be in the absence of the disease. Factoring in additional costs of undiagnosed DM, prediabetes, and gestational DM brings the total costs of DM to \$218 billion, with \$18 billion for people with undiagnosed DM, \$25 billion for adults with prediabetes, and \$623 million for women with gestational DM.<sup>1</sup> The burden of DM is imposed on all sectors of society, through, for example, higher insurance premiums paid by employees and employers, reduced earnings as a result of productivity loss, and reduced overall quality of life for patients and their families.<sup>2</sup>

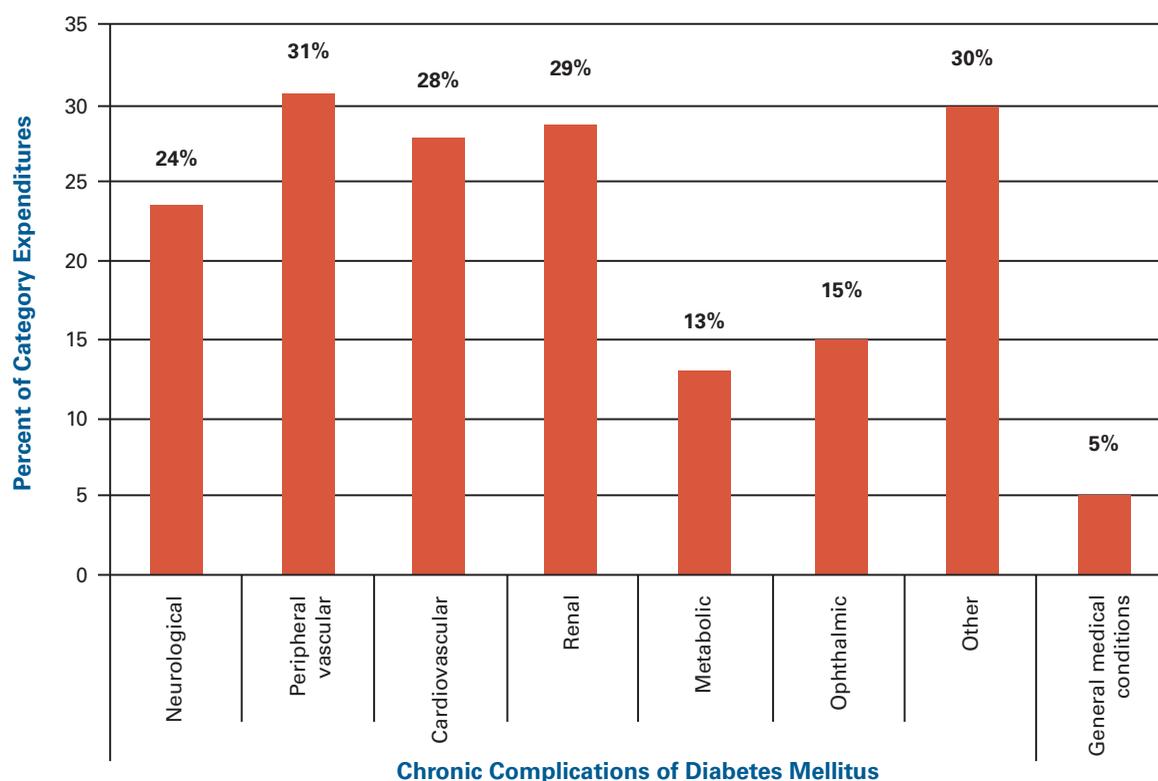
In broad terms, the most recognized pathophysiologic defects in T2DM are decreased insulin secretion and insulin resistance, but in order to fully examine these and other

pathophysiologic origins of DM, it is critical to review the mechanisms involved in normal and abnormal glucose homeostasis.

### Normal Glucose Homeostasis

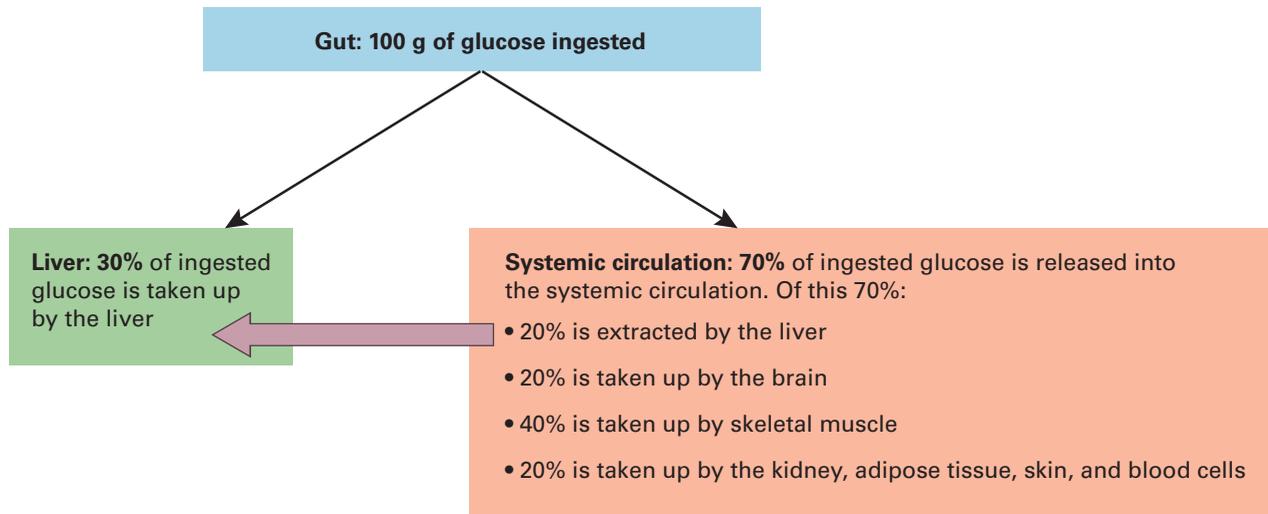
Glucose, a fundamental source of cellular energy, is released by the breakdown of endogenous glycogen stores that are primarily located in the liver. Glucose is also released indirectly in the muscle through intermediary metabolites. These whole-body energy stores are replenished from dietary glucose, which, after being digested and absorbed across the gut wall, is distributed among the various tissues of the body.<sup>3</sup> Although glucose is required by all cells, its main consumer is the brain in the fasting or “postabsorptive” phase, which accounts for approximately 50% of the body’s glucose use. Another 25% of glucose disposal occurs in the splanchnic area (liver and gastrointestinal tissue), and the remaining 25% takes place in insulin-dependent tissues, including muscle and adipose tissue.<sup>4</sup> Approximately 85% of endogenous glucose production is derived from the liver, with glycogenolysis (conversion of glycogen to glucose) and gluconeogenesis (glucose formation) contributing equally to

■ **Figure 1.** Percent of Category Expenditures Associated With Diabetes Mellitus Complications<sup>2</sup>



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■ **Figure 2.** Glucose Disposal by Various Tissues After a Hypothetical Meal Containing 100 g of Glucose<sup>8</sup>



When 100 g of glucose is ingested, 30% is taken up by the liver and 70% is released into the systemic circulation. Of this 70 g, 15 g (20%) is extracted by the liver, 15 g (20%) is taken up by the brain, 27 g (40%) is taken up by skeletal muscle, and the remaining 20% is taken up by kidney, adipose tissue, skin, and blood cells.

Adapted from Gerich JE. *Diabetes Obes Metab.* 2000;2:345-350.

the basal rate of hepatic glucose production. The remaining ~15% of glucose is produced by the kidneys.<sup>4</sup>

Normally, following glucose ingestion, the increase in plasma glucose concentration triggers insulin release, which stimulates splanchnic and peripheral glucose uptake and suppresses endogenous (primarily hepatic) glucose production. In healthy adults, blood glucose levels are tightly regulated within a range of 70 to 99 mg/dL, and maintained by specific hormones (eg, insulin, glucagon, incretins) as well as the central and peripheral nervous system, to meet metabolic requirements.<sup>5-7</sup> Various cells and tissues (within the brain, muscle, gastrointestinal tract, liver, kidney, and adipose tissue) are also involved in blood glucose regulation by means of uptake, metabolism, storage, and excretion (Figure 2).<sup>4,6-8</sup> This highly controlled process of glucose regulation may be particularly evident during the postprandial period, during which, under normal physiologic circumstances, glucose levels rarely rise beyond 140 mg/dL, even after consumption of a high-carbohydrate meal.<sup>6</sup>

Among the various hormones involved in glucose regulation, insulin and glucagon (both produced in the pancreas by islets of Langerhans) are the most relevant.<sup>7</sup> Within the islets of Langerhans,  $\beta$ -cells produce insulin and  $\alpha$ -cells produce glucagon. Insulin, a potent antilipolytic (inhibiting fat breakdown) hormone, is known to reduce blood glucose levels by accelerating transport of glucose into insulin-sensitive

cells and facilitating its conversion to storage compounds via glycogenesis (conversion of glucose to glycogen) and lipogenesis (fat formation).<sup>7</sup> Glucagon, which also plays a central role in glucose homeostasis, is produced in response to low normal glucose levels or hypoglycemia and acts to increase glucose levels by accelerating glycogenolysis and promoting gluconeogenesis.<sup>7</sup> After a glucose-containing meal, however, glucagon secretion is inhibited by hyperinsulinemia, which contributes to suppression of hepatic glucose production and maintenance of normal postprandial glucose tolerance.<sup>7</sup> The hormone amylin contributes to reduction in postprandial glucagon, as well as modest slowing of gastric emptying.<sup>9</sup>

Incretins, which include glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are also involved in regulation of blood glucose, in part by their effects on insulin and glucagon.<sup>9,10</sup> However, both GLP-1 and GIP are considered glucose-dependent hormones, meaning that they are secreted only when glucose levels rise above normal fasting plasma glucose levels; they do not directly stimulate insulin secretion. Normally, these hormones are released in response to meals and, by activating certain receptors (G protein-coupled) on pancreatic  $\beta$ -cells, they aid in stimulation of insulin secretion. When glucose levels are low, however, GLP-1 and GIP levels (and their stimulating effects on insulin secretion) are diminished.<sup>11</sup>

### Transport of Glucose Into Cells

Since glucose cannot readily diffuse through (impermeable) cell membranes, it requires assistance from both insulin and a family of transport proteins (facilitated glucose transporter [GLUT] molecules) in order to gain entry into most cells.<sup>3</sup> Essentially, GLUTs act as shuttles, forming an aqueous pore across otherwise hydrophobic cellular membranes, through which glucose can move more easily.<sup>3</sup> Of the 12 known GLUT molecules, GLUT4 is considered the major transporter for adipose, muscle, and cardiac tissue, whereas GLUTs 1, 2, 3, and 8 facilitate glucose entry into other organs (eg, brain, liver), though we continue to learn more about the role of GLUTs in DM.<sup>6,7,12</sup> Activation of GLUT4 and, in turn, facilitated glucose diffusion into muscle and adipose tissue, is dependent on the presence of insulin, whereas the function of other GLUTs is more independent of insulin.<sup>7,13</sup> Once glucose enters cells, it is phosphorylated (via glucokinase in the liver and hexokinase in most other cells), after which it cannot diffuse out of cells and can then be either used for energy production or converted to a storage compound (ie, glycogen, fat).<sup>4,6</sup>

### Major Systems Involved in Glucose Utilization and Regulation

The majority of glucose uptake ( $\geq 80\%$ ) in peripheral tissue occurs in muscle, where glucose may either be used immediately for energy or stored as glycogen.<sup>6</sup> As stated previously, skeletal muscle is insulin-dependent, and thus requires insulin for activation of the major enzyme (glycogen synthase) that regulates production of glycogen.<sup>10</sup> While adipose tissue is responsible for a much smaller amount of peripheral glucose uptake (2%-5%), it plays an important role in the maintenance of total body glucose homeostasis by regulating the release of free fatty acids (which increase gluconeogenesis) from stored triglycerides, influencing insulin sensitivity in the muscle and liver.<sup>4</sup>

While the liver does not require insulin to facilitate glucose uptake, it does need insulin to regulate glucose output.<sup>4</sup> So, for example, when insulin concentrations are low, hepatic glucose output rises.<sup>10</sup> Additionally, insulin helps the liver store most of the absorbed glucose in the form of glycogen.<sup>6</sup>

The kidneys are increasingly recognized to play an important role in glucose homeostasis via release of glucose into the circulation (gluconeogenesis), uptake of glucose from the circulation to meet renal energy needs, and reabsorption of glucose at the proximal tubule.<sup>12</sup> The kidneys also aid in elimination of excess glucose (when levels exceed approximately 180 mg/dL, though this threshold may rise during chronic hyperglycemia) by facilitating its excretion in the

urine.<sup>2</sup> In DM, where glucose levels are high and may exceed the threshold of glucose reabsorption, more glucose may be excreted in the urine if concentrations in filtered urine become high.<sup>6</sup>

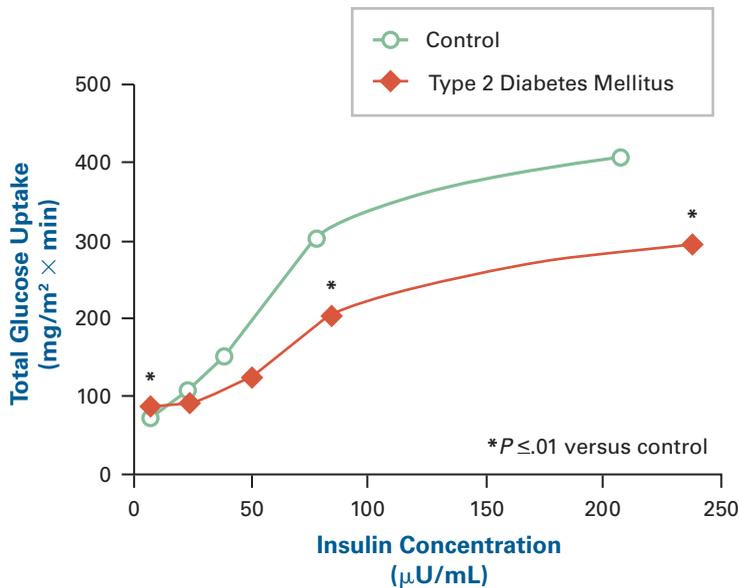
### Pathophysiology of T2DM

DM is a group of metabolic diseases characterized by hyperglycemia. The hallmark state of chronic hyperglycemia is associated with long-term damage, dysfunction, and potential failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.<sup>14</sup> Numerous factors contribute to the development of T2DM, with the central defects being inadequate insulin secretion (insulin deficiency) and/or diminished tissue responses to insulin (insulin resistance) at 1 or more points in the complex pathways of hormone action.<sup>14</sup> Insulin deficiency and insulin resistance frequently coexist, though the contribution to hyperglycemia can vary widely along the spectrum of T2DM.

The pancreas has a remarkable capacity to adapt to conditions of increased insulin demand (eg, in obesity, pregnancy, cortisol excess) to maintain normoglycemia. Compensatory hyperinsulinemia maintains glucose homeostasis. However, when  $\beta$ -cell secretion of insulin becomes inadequate for the glucose load, hyperglycemia occurs. Progressive deterioration in  $\beta$ -cell function and mass is well known to occur over time in T2DM and the resultant state of impaired insulin secretion is found uniformly in T2DM patients of all ethnic backgrounds.<sup>4,15</sup> Research has shown that at time of diagnosis, islet cell function/responsiveness to glucose is approximately 30% to 50% of normal, and  $\beta$ -cell mass is reduced by about 60%; both of these are important determinants of the amount of insulin that is secreted.<sup>4</sup> Based on analyses from the United Kingdom Prospective Diabetes Study, a direct correlation exists between progressive loss in  $\beta$ -cell function and poor glycemic control (as measured by A1C levels).<sup>16</sup> The major factors implicated in progressive loss of  $\beta$ -cell function and mass include glucotoxicity, lipotoxicity, proinflammatory cytokines, leptin, and islet cell amyloid. Research indicates that progressive impaired  $\beta$ -cell function and possibly  $\beta$ -cell mass may be arrested, though clinical evidence in humans remains scarce.<sup>15</sup>

Impaired insulin secretion is often exacerbated by insulin resistance, which is characterized by the inability of insulin to decrease plasma glucose levels through suppression of hepatic glucose production and stimulation of glucose utilization in skeletal muscle and adipose tissue.<sup>10</sup> In the presence of physiologically possible levels of insulin in humans, there is decreased glucose uptake in subjects with T2DM versus normal subjects, confirming that glucose uptake is severely

■ **Figure 3.** Plasma Insulin Concentration and Whole Body Glucose Uptake<sup>17</sup>



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impaired due to insulin resistance (Figure 3).<sup>4,17</sup> As a consequence of insulin resistance, inefficient glucose utilization is eventually replaced by cellular utilization of fats and proteins for energy. Insulin resistance is contributed to by genetic and environmental factors. Family history can contribute directly to insulin resistance, but multiple environmental factors such as obesity, comorbidities, and central adiposity (visceral) can all contribute. The exact cause of insulin resistance in any given patient is complex, but may include defects in insulin-mediated cell signaling pathways, reduced insulin-stimulated muscle glycogen synthesis,<sup>18</sup> or even potentially fewer insulin receptors (particularly in skeletal muscle, liver, and adipose tissue in obese subjects).<sup>6</sup>

The relative contribution of insulin secretion and insulin resistance to the development of hyperglycemia may differ due to the heterogeneity of T2DM. Under most circumstances, insulin resistance is the earliest detectable defect in individuals with prediabetes.<sup>19</sup> Initially, enhanced insulin secretion may compensate for the insulin resistance; however, early phase insulin secretion is impaired. In the transition from normal glucose tolerance to impaired glucose tolerance and DM, insulin sensitivity deteriorates about 40%, whereas insulin secretion deteriorates 3- to 5-fold.<sup>19</sup> In DM, chronic hyperglycemia may result in further deterioration of insulin sensitivity and secretion (glucotoxicity), which is aggravated by elevated free fatty acids (lipotoxicity).<sup>19</sup>

Other increasingly more well-understood mechanisms contributing to the pathophysiology of T2DM include increased hepatic glucose output and adipocyte dysfunction. Following glucose ingestion, insulin is normally secreted into the portal vein, where it is taken up by the liver and suppresses hepatic glucose output. However, if the liver does not perceive this insulin signal and continues to produce glucose, the 2 sources of glucose input (from the liver and the gastrointestinal tract) will result in marked hyperglycemia.<sup>4</sup> The increased hepatic glucose output seen in T2DM is thought to be related partly to insulin resistance and is closely correlated with the severity of fasting hyperglycemia. To the latter

point, it has been shown that while the postabsorptive level of chronic hyperinsulinemia seen in mild hyperglycemia ( $\leq 140$  mg/dL) is enough to offset hepatic insulin resistance and maintain a normal basal rate of hepatic glucose output, moderate fasting hyperglycemia is associated with significant increases in hepatic glucose output.<sup>4</sup> In individuals with T2DM with overt fasting hyperglycemia ( $\geq 140$  mg/dL), an excessive rate of hepatic glucose output is considered the major abnormality responsible for the elevated fasting plasma glucose.<sup>4</sup> Although hyperinsulinemia and hyperglycemia (both certainly present in T2DM) are potent inhibitors of hepatic glucose output, they do not appear to fully correct excessive glucose output by the liver, which is suggestive of existing hepatic resistance to insulin and potential hyperglucagonemia contributing to an elevated plasma glucose.<sup>4</sup>

With regard to adipocyte dysfunction, considerable evidence implicates deranged metabolism and altered disposition of fat in the pathogenesis of glucose intolerance in T2DM.<sup>20</sup> Because fat cells are resistant to insulin's antilipolytic effect, the resultant chronically elevated plasma free fatty acid levels stimulate gluconeogenesis, induce hepatic/muscle insulin resistance, and impair insulin secretion in predisposed individuals.<sup>20</sup> These free fatty acid-induced disturbances are referred to as lipotoxicity. Beyond this phenomenon, dysfunctional fat cells also produce excessive amounts of insulin resistance-inducing, inflammatory, and atherosclerotic-provoking cytokines and fail to secrete

normal amounts of insulin-sensitizing adipocytokines (adiponectin).<sup>20</sup> Also, the pattern of fat disposition in T2DM is abnormal, essentially because enlarged adipocytes (in visceral fat) are insulin-resistant and have diminished capacity to store fat, which leads to lipid overflow into muscle, liver, and potentially  $\beta$ -cells, further exacerbating muscle/hepatic insulin resistance and impaired insulin secretion. They are also major sources of proinflammatory adipocytokines. Within liver cells, the elevated free fatty acids are converted to triglycerides, which accumulate and cause steatosis (or fatty liver) and consequently may increase the chances of nonalcoholic steatohepatitis (NASH) and even cirrhosis.<sup>10</sup> These disturbances in adipocyte function are particularly relevant in light of the fact that many individuals with T2DM are obese.

The development of glucose intolerance in T2DM involves multiple systems including the muscle, liver,  $\beta$ -cell, fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance),  $\alpha$ -cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance).<sup>21</sup> Collectively, these 8 players comprise the ominous octet and dictate the need for combination therapy. Treatment should be based upon reversal of known pathogenic abnormalities and should not be directed simply at the reduction of A1C. Early initiation of therapy may help to prevent or slow progressive  $\beta$ -cell failure.<sup>21</sup>

### Clinical Manifestations of T2DM

The majority of patients with T2DM are either obese (with obesity itself contributing to insulin resistance) or have an increased proportion of body fat in the abdominal region. Many factors increase the risk of developing T2DM, including family history, age, obesity, and lack of physical activity. Also, DM occurs more frequently in women with prior gestational DM and in individuals with hypertension or dyslipidemia.<sup>14</sup> T2DM is frequently undiagnosed for many years, since the hyperglycemia develops gradually and, at least in the early stages, is not severe enough to cause clinical symptoms. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, polyphagia, and blurred vision.<sup>14</sup>

Although the degree of hyperglycemia seen with T2DM may not cause symptoms initially, it is sufficient to cause pathologic and functional changes in target tissues, and as such, will increase the risk of microvascular and macrovascular complications.<sup>14</sup> Hyperglycemia, or long-term glycemic burden, appears to be cumulative, increasing the chances of complications with longer exposure. These long-term complications include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy

■ **Table.** Major Factors Responsible for Maintenance of Normal Glucose Tolerance in Healthy Subjects<sup>4</sup>

#### Insulin secretion

##### Tissue glucose uptake

- Peripheral (primarily muscle)
- Splanchnic (liver plus gut)

##### Suppression of hepatic glucose production

- Decreased free fatty acids
- Decreased glucagon

#### Route of glucose administration

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with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Diabetic patients also have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease.<sup>14</sup>

### Summary

Glucose, a vital energy source for many cells and tissues, is tightly regulated via a complex interaction between pancreatic  $\beta$ -cells and  $\alpha$ -cells, associated organs (eg, intestines, liver, skeletal muscle, adipose tissue), and respective hormones (ie, insulin, glucagon, GLP-1, GIP, amylin, and others). A summary of the major factors responsible for maintenance of normal glucose tolerance in healthy subjects is provided in the **Table**.<sup>4</sup> Beyond these primary controllers of glucose regulation, incretin hormones (GIP and GLP-1) further assist in maintenance of normal plasma glucose and a host of transport proteins (GLUT molecules) facilitate movement of glucose through otherwise impermeable cellular membranes. The primary tissues involved in glucose utilization include the brain, muscle, fat, and the splanchnic area, with muscle tissue comprising the most important site of peripheral glucose uptake.

Knowledge of the fundamentals of normal glucose homeostasis is essential to understanding the pathophysiologic derangements that may result from glucose imbalance disorders. Conditions such as T2DM are characterized by an imbalance in glucose regulation, causing chronic hyperglycemia and ultimately leading to multiorgan damage. Several factors are implicated in the development of T2DM, including insulin resistance, insulin deficiency, increased hepatic glucose production, and adipocyte dysfunction. An increasingly clear understanding of these derangements has helped both researchers and clinicians to better manage T2DM and improve clinical outcomes.

## Reports

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