# Diabetes Mellitus

## I. OVERVIEW OF DIABETES MELLITUS

Diabetes is not one disease, but rather is a heterogeneous group of syndromes characterized by an elevation of fasting blood glucose caused by a relative or absolute deficiency in insulin. Diabetes mellitus is the leading cause of adult blindness and amputation, and a major cause of renal failure, heart attacks, and strokes. Most cases of diabetes mellitus can be separated into two groups (Figure 25.1), type 1 (formerly called insulin-dependent diabetes mellitus) and type 2 (formerly called non-insulin-dependent diabetes mellitus). Approximately 30,000 newly-diagnosed cases of type 1 and 625,000 cases of type 2 diabetes mellitus are estimated to occur yearly in the United States. The incidence and prevalence of type 2 disease is increasing because of the aging of the United States population, and the increasing prevalence of obesity and sedentary lifestyles. The increase in children with type 2 diabetes is particularly disturbing.

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE OF ONSET</strong></td>
<td>Usually during childhood or puberty; symptoms develop rapidly</td>
<td>Frequently after age 35; symptoms develop gradually</td>
</tr>
<tr>
<td><strong>NUTRITIONAL STATUS AT TIME OF DISEASE ONSET</strong></td>
<td>Frequently undernourished</td>
<td>Obesity usually present</td>
</tr>
<tr>
<td><strong>PREVALENCE</strong></td>
<td>900,000 = 10% of diagnosed diabetics</td>
<td>10 Million = 90% of diagnosed diabetics</td>
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<tr>
<td><strong>GENETIC PREDISPOSITION</strong></td>
<td>Moderate</td>
<td>Very strong</td>
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<tr>
<td><strong>DEFECT OR DEFICIENCY</strong></td>
<td>β Cells are destroyed, eliminating production of insulin</td>
<td>Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin</td>
</tr>
<tr>
<td><strong>FREQUENCY OF KETOsis</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>PLASMA INSULIN</strong></td>
<td>Low to absent</td>
<td>High early in disease; low in disease of long duration</td>
</tr>
<tr>
<td><strong>ACUTE COMPLICATIONS</strong></td>
<td>Ketoacidosis</td>
<td>Hyperosmolar state</td>
</tr>
<tr>
<td><strong>TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS</strong></td>
<td>Unresponsive</td>
<td>Responsive</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Insulin is always necessary</td>
<td>Diet, exercise, oral hypoglycemic drugs, ± insulin</td>
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</table>

*Figure 25.1*
Comparison of type 1 and type 2 diabetes.
II. TYPE 1 DIABETES

Persons with type 1 diabetics constitute approximately ten percent of the ten million known diabetics in the United States. The disease is characterized by an absolute deficiency of insulin caused by an autoimmune attack on the β cells of the pancreas. In type 1 diabetes, the islets of Langerhans become infiltrated with activated T lymphocytes, leading to a condition called insulinitis. Over a period of years, this autoimmune attack on the β cells leads to gradual depletion of the β cell population (Figure 25.2). However, symptoms appear abruptly when eighty to ninety percent of the β cells have been destroyed. At this point, the pancreas fails to respond adequately to ingestion of glucose, and insulin therapy is required to restore metabolic control and prevent life-threatening ketoacidosis. β Cell destruction requires both a stimulus from the environment (such as a viral infection) and a genetic determinant that allows the β cells to be recognized as “non-self.” [Note: Among monozygotic (identical) twins, if one sibling develops type 1 diabetes mellitus, the other twin has only a thirty to fifty percent chance of developing the disease. This contrasts with type 2 disease (see p. 340), in which the genetic influence is stronger, and in virtually all monozygotic twinships, the disease develops in both individuals.]

A. Diagnosis of type 1 diabetes

The onset of type 1 diabetes is typically during childhood or puberty, and symptoms develop rapidly. Patients with type 1 diabetes can usually be recognized by the abrupt appearance of polyuria (frequent urination), polydipsia (excessive thirst), and polyphagia (excessive hunger), often triggered by stress or an illness. These symptoms are usually accompanied by fatigue, weight loss, and weakness. The diagnosis is confirmed by a fasting blood glucose (FBG) greater than or equal to 126 mg/dl, commonly accompanied by ketoacidosis. [Note: a FBG between 100-125 mg/dl is categorized as an impaired FBG.] Fasting is defined as no caloric intake for at least 8 hours. When the diagnosis of type 1 diabetes is uncertain by clinical presentation, testing for circulating islet-cell antibodies is recommended. Oral glucose tolerance test as a diagnostic tool for diabetes has fallen into disfavor because it is time-consuming and the results are highly variable.

B. Metabolic changes in type 1 diabetes

The metabolic abnormalities of diabetes mellitus result from a deficiency of insulin which profoundly affects metabolism in three tissues: liver, muscle, and adipose tissue (Figure 25.3).

1. Hyperglycemia and ketoacidosis: Elevated levels of blood glucose and ketones are the hallmarks of untreated type 1 diabetes melli-
Figure 25.3
Inter-tissue relationships in type 1 diabetes.

Hyperglycemia results from increased hepatic gluconeogenesis and decreased glucose uptake by insulin-dependent GLUT4s of adipose tissue and muscle.

Ketosis results from the massive mobilization of fatty acids from the adipose followed by hepatic ketogenesis.

2. Hypertriacylglycerolemia: Not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. These excess fatty acids are converted to triacylglycerol, which is packaged and secreted in very-low-density lipoproteins (VLDL). Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal (see p. 175). Because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low
in diabetics (synthesis of the enzyme is decreased when insulin levels are low), the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia (see Figure 25.3).

C. Treatment of type 1 diabetes

Type 1 diabetes must rely on exogenous insulin injected subcutaneously to control the hyperglycemia and ketoacidosis. Two therapeutic regimens are currently in use—standard and intensive insulin treatment.

Insulin may also be delivered by an pump, which allows continued infusion of insulin 24 hours a day at preset levels and the ability to program doses (a bolus) of insulin as needed at meal times. It is also possible to administer insulin as an inhaled powder.

1. Standard treatment versus intensive treatment: Standard treatment typically consists of one or two daily injections of insulin. Mean blood glucose levels obtained are typically in the 225 to 275 mg/dl range, with an HbA1C (see p. 34) of eight to nine percent of the total hemoglobin (blue arrow, Figure 25.4). [Note: The rate of formation of HbA1C is proportional to the average blood glucose concentration over the previous several months. Thus, HbA1C provides a measure of how well treatment has normalized blood glucose in the diabetic over that time.] In contrast to standard therapy, intensive treatment seeks to more closely normalize blood glucose through more frequent monitoring, and subsequent injections of insulin—typically three or more times a day. Mean blood glucose levels of 150 mg/dl can be achieved, with HbA1C approximately seven percent of the total hemoglobin (red arrow, see Figure 25.4). [Note: Normal mean blood glucose is approximately 110 mg/dl and HbA1C is six percent or less (black arrow, see Figure 25.4).] Thus, normalization of glucose values (euglycemia) is not achieved even in intensively treated patients. Nonetheless, patients on intensive therapy showed a sixty percent reduction in the long-term microvascular complications of diabetes—retinopathy, nephropathy, and neuropathy—compared with patients receiving standard care. This confirms that the complications of diabetes are related to an elevation of plasma glucose.

2. Hypoglycemia in type 1 diabetes: One of the therapeutic goals of diabetes is to decrease blood glucose levels in an effort to minimize the development of the long-term complications of the disease (see p. 343 for a discussion of the chronic complications of diabetes). However, appropriate dosage is difficult to achieve. Hypoglycemia caused by excess insulin is the most common complication of insulin therapy, occurring in more than ninety percent of patients. The frequency of hypoglycemic episodes, coma, and seizures is particularly high with intensive treatment regimens designed to achieve tight control of blood glucose (Figure 25.5). Recall that in
normal individuals hypoglycemia triggers a compensatory secretion of counterregulatory hormones, most notably glucagon and epinephrine, which promote hepatic production of glucose. However, patients with type 1 diabetes also develop a deficiency of glucagon secretion. This defect occurs early in the disease and is almost universally present four years after diagnosis. These patients thus rely on epinephrine secretion to prevent severe hypoglycemia. However, as the disease progresses, type 1 diabetes patients show diabetic autonomic neuropathy and impaired ability to secrete epinephrine in response to hypoglycemia. The combined deficiency of glucagon and epinephrine secretion creates a condition sometimes called “hypoglycemia unawareness.” Thus, patients with longstanding diabetes are particularly vulnerable to hypoglycemia. Hypoglycemia can also be caused by strenuous exercise. Exercise promotes glucose uptake into muscle and decreases the need for exogenous insulin. Patients should, therefore, check blood glucose levels before or after intensive exercise to prevent or abort hypoglycemia.

3. Contraindications for tight control: Children are not put on a program of tight control of blood glucose because of the risk that episodes of hypoglycemia may adversely affect brain development. Elderly people typically do not go on tight control. Hypoglycemia can cause strokes and heart attacks in older people. Also, the major goal of tight control is to prevent complications many years later.

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**III. TYPE 2 diabetes**

Type 2 diabetes is the most common form of the disease, afflicting approximately ninety percent of the diabetic population in the United States. Typically, type 2 diabetes develops gradually without obvious symptoms. The disease is often detected by routine screening tests. However, many individuals with type 2 diabetes have symptoms of polyuria and polydipsia of several weeks duration. Polyphagia may be present, but is less common. Patients with type 2 diabetes have a combination of insulin resistance and dysfunctional β cells (Figure 25.6), but do not require insulin to sustain life, although insulin may be required to control hyperglycemia in some patients. The metabolic alterations observed in type 2 diabetes are milder than those described for type 1, in part, because insulin secretion in type 2 diabetes—although not adequate—does restrain ketogenesis and blunts the development of diabetic ketoacidosis. Diagnosis is based most commonly on the presence of hyperglycemia—that is, a blood glucose concentration of equal to or greater than 126 mg/dl. Pathogenesis does not involve viruses or autoimmune antibodies.

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**Figure 25.6**

Major factors contributing to hyperglycemia observed in type 2 diabetes.
A. Insulin resistance

Insulin resistance is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal circulating concentrations of insulin. For example, insulin resistance is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.

1. Insulin resistance and obesity: Obesity is the most common cause of insulin resistance. Most people with obesity and insulin resistance do not become diabetic. In the absence of a defect in β cell function, non-diabetic, obese individuals can compensate for insulin resistance with elevated levels of insulin. For example, Figure 25.7A shows that insulin secretion is two to three times higher in obese subjects than it is in lean individuals. This higher insulin concentration compensates for the diminished effect of the hormone (as a result of insulin resistance), and produces blood glucose levels similar to those observed in lean individuals (Figure 25.7B).

2. Insulin resistance and type 2 diabetes: Insulin resistance alone will not lead to type 2 diabetes. Rather, type 2 diabetes develops in insulin-resistant individuals who also show impaired β cell function. Insulin resistance and subsequent development of type 2 diabetes is commonly observed in the elderly, and in individuals who are obese, physically inactive, or in women who are pregnant (gestational diabetes which is seen in 3-5% of pregnant women). These patients are unable to sufficiently compensate for insulin resistance with increased insulin release. Figure 25.8 shows the time course for the development of hyperglycemia and the loss of β cell function.

![Figure 25.7](image)

Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.
3. Causes of insulin resistance: Insulin resistance increases with weight gain and, conversely, diminishes with weight loss. This suggests that fat accumulation is important in the development of insulin resistance. Adipose tissue is not simply an energy storage organ, but also a secretory organ. Regulatory substances produced by adipocytes include leptin (see p. 350), resistin (see p. 351), and adiponectin (see p. 351), all of which may contribute to the development of insulin resistance. In addition, the elevated levels of free fatty acids that occur in obesity have also been implicated in the development of insulin resistance.

B. Dysfunctional β cells

In type 2 diabetes, the pancreas initially retains β cell capacity, resulting in insulin levels that vary from above normal to below normal. However, with time, the β cell becomes increasingly dysfunctional and fails to secrete enough insulin to correct the prevailing hyperglycemia. For example, insulin levels are high in typical, obese, type 2 diabetics patients, but not as high as in similarly obese individuals who are non-diabetic. Thus, the natural progression of the disease results in a declining ability to control hyperglycemia with endogenous secretion of
insulin (Figure 25.9). Deterioration of β cell function may be accelerated by the toxic effects of sustained hyperglycemia and elevated free fatty acids.

C. Metabolic changes in type 2 diabetes

The metabolic abnormalities of type 2 diabetes mellitus are the result of insulin resistance expressed primarily in liver, muscle, and adipose tissue (Figure 25.10).

1. Hyperglycemia: Hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral use. Ketosis is usually minimal or absent in type 2 patients because the presence of insulin—even in the presence of insulin resistance—diminishes hepatic ketogenesis.

2. Hypertriacylglycerolemia: In the liver, fatty acids are converted to triacylglycerols, which are packaged and secreted in VLDLs. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal (see p. 175). Because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue (see p. 226) is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia (see Figure 25.10).

D. Treatment of type 2 diabetes

The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits, and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modifications often correct the hyperglycemia of type 2 diabetes. Hypoglycemic agents1 or insulin therapy may be required to achieve satisfactory plasma glucose levels.

IV. CHRONIC EFFECTS AND PREVENTION OF DIABETES

As noted previously, available therapies moderate the hyperglycemia of diabetes, but fail to completely normalize metabolism. The long-standing elevation of blood glucose causes the chronic complications of dia-

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be—premature atherosclerosis (including cardiovascular disease and stroke), retinopathy, nephropathy, and neuropathy. Intensive treatment with insulin (see p. 339) delays the onset and slows the progression of these long-term complications. For example, the incidence of retinopathy decreases as control of blood glucose improves and HbA1C levels decrease (Figure 25.11). The benefits of tight control of blood glucose outweigh the increased risk of severe hypoglycemia. How hyperglycemia causes the chronic complications of diabetes is unclear. In cells where entry of glucose is not dependent on insulin, elevated blood glucose leads to increased intracellular glucose and its metabolites. For example, increased intracellular sorbitol contributes to the formation of cataracts (see p. 138). Further, hyperglycemia promotes the condensation of glucose with cellular proteins in a reaction analogous to the formation of HbA1C (see p. 34). These glycated proteins mediate some of the early microvascular changes of diabetes. There is currently no preventative treatment for type 1 diabetes. The risk for type 2 diabetes can be significantly decreased by a combined regimen of medical nutrition therapy, weight loss, and exercise. For example, Figure 25.12 show the
The benefits of an improvement in glycemic control occurred over the entire range of HbA1c values; thus, any improvement in glycemic control is beneficial.

Figure 25.11
Relationship of glycemic control and diabetic retinopathy.

The incidence of disease in normal and overweight individuals with varying degrees of exercise. Other risk factors for the disease include hypertension and elevated blood lipids. The benefits of tight control of blood glucose levels has been shown in patients with type 1 diabetes, but most expert believe that tight control can also prevent complications in people with type 2 diabetes.

V. CHAPTER SUMMARY

Diabetes mellitus is a heterogeneous group of syndromes characterized by an elevation of fasting blood glucose that is caused by a relative or absolute deficiency in insulin. Diabetes is the leading cause of adult blindness and amputation, and a major cause of renal failure, heart attacks, and stroke. The disease can be classified into two groups, type 1 and type 2. Type 1 diabetics constitute approximately ten percent of diabetics in the United States. The disease is characterized by an absolute deficiency of insulin caused by an autoimmune attack on the β cells of the pancreas. This destruction requires a stimulus from the environment (such as a viral infection) and a genetic determinant that allows the β cell to be recognized as “non-self.” The metabolic abnormalities of type 1 diabetes mellitus include hyperglycemia, ketoacidosis, and hypertriacylglycerolemia. They result from a deficiency of insulin and a relative excess of glucagon. Type 1 diabetics must rely on exogenous insulin injected subcutaneously to control hyperglycemia and ketoacidosis. Type 2 diabetes has a strong genetic component. It results from a combination of insulin resistance and dysfunctional β cells. Insulin resistance is the decreased ability of target tissues, such as liver, adipose tissue and muscle, to respond properly to normal circulating concentrations of insulin. Obesity is the most common cause of insulin resistance. However, most people with obesity and insulin resistance do not become diabetic. In the absence of a defect in β cell function, non-diabetic, obese individuals can compensate for insulin resistant with elevated levels of insulin. Insulin resistance alone will not lead to type 2 diabetes. Rather, type 2 diabetes develops in insulin-resistant individuals who also show impaired β cell function. The metabolic alterations observed in type 2 diabetes are milder than those described for the insulin-dependent form of the disease, in part, because insulin secretion in type 2 diabetes—although not adequate—does restrain ketogenesis and blunts the development of diabetic ketoacidosis. Available treatments for diabetes moderate the hyperglycemia, but fail to completely normalize metabolism. The long-standing elevation of blood glucose causes the chronic complications of diabetes—premature atherosclerosis, retinopathy, nephropathy, and neuropathy.

Figure 25.12
**V. Chapter Summary**

**Type 1 diabetes**
- Associated with immunologic trigger
- Leads to autoimmune destruction of β cells in individuals with a genetic predisposition
- Leads to loss of insulin secretory capacity
- Type 1 diabetes often exhibits polyuria, polydipsia, and polyphagia

**Type 2 diabetes**
- Associated with obesity
- Leads to insulin resistance
- Characterized by hyperinsulinemia
- Decline of β-cell function

**Absolute or relative deficiency of insulin**
- Characterized by abnormal metabolism
- Breakdown of tissue proteins
- Glycogenolysis
- Glucose uptake by tissues
- Gluconeogenesis
- Hepatic output of glucose
- Hyperglycemia

**Ketoacidosis**
- Free fatty acids in plasma
- Lipolysis
- Hepatic output of ketone bodies

**Prevalence of diabetes and its risk factors**
- U.S. population (300 million)
- Obesity and insulin resistance (80 million)
- Type 2 diabetes (10 million diagnosed, plus 10 million undiagnosed)
- Type 1 diabetes (900,000)

**Key concept map for diabetes.**
Study Questions

Choose the ONE correct answer

25.1 Relative or absolute lack of insulin in humans would result in which one of the following reactions in the liver?
   A. Increased glycogen synthesis
   B. Decreased gluconeogenesis from lactate
   C. Decreased glycogenolysis
   D. Increased formation of 3-hydroxybutyrate
   E. Decreased action of hormone-sensitive lipase

   Correct answer = D. Low insulin levels favor the liver producing ketone bodies, using acetyl CoAs it obtained from excess fatty acids provided by the adipose. Low insulin also causes activation of hormone-sensitive lipase, decreased glycerol synthesis, and increased gluconeogenesis.

25.2 Which one of the following is most often found in untreated patients with type 1 and type 2 diabetes?
   A. Hyperglycemia
   B. Extremely low levels of insulin synthesis and secretion
   C. Synthesis of an insulin with an abnormal amino acid sequence
   D. A simple pattern of genetic inheritance
   E. Ketoacidosis

   Correct answer = A. Elevated blood glucose occurs in type 1 diabetes as a result of a lack of insulin. In type 2 diabetes, hyperglycemia is due to a defect in β cell function and insulin resistance. Both forms of the disease show complex genetics. Ketoacidosis is more common in type 1 disease.

25.3 An obese individual with type 2 diabetes:
   A. usually shows a normal glucose tolerance test.
   B. usually has a lower plasma level of insulin than a normal individual.
   C. usually shows significant improvement in glucose tolerance if body weight is reduced to normal.
   D. usually benefits from receiving insulin about six hours after a meal.
   E. usually has lower plasma levels of glucagon than a normal individual.

   Correct answer = C. Eighty percent of type 2 diabetics are obese, and almost all show some improvement in blood glucose with weight reduction. These patients show an abnormal glucose tolerance test, have elevated insulin levels, and usually do not require insulin (certainly not six hours after a meal). Glucagon levels are typically normal.

25.4 An individual with insulin resistance:
   A. usually shows elevated fasting glucose levels.
   B. usually shows elevated fasting insulin levels.
   C. will eventually become diabetic.
   D. is rarely obese.
   E. is treated by injection of insulin.

   Correct answer = B. Insulin resistance is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal circulating concentrations of insulin. Obesity is the most common cause of insulin resistance. Most of the people with obesity and insulin resistance do not become diabetic. In the absence of a defect in β cell function, non-diabetic, obese individuals can compensate for insulin resistance with elevated levels of insulin. The elevated insulin levels normalize fasting blood glucose levels. Insulin resistance without overt diabetes requires no pharmacological treatment.