# Diabetes Mellitus: Pathogenesis and Treatment Strategies

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This article introduces the disease state of diabetes mellitus and provides a background of the impact of the disease on the population, its biology and pathophysiology, and the current treatment strategies for treating diabetes.

## Burden of Diabetes

Diabetes mellitus is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to increase to 220 million people by 2010.[1] It is principally recognized by elevation of plasma glucose or hyperglycemia. In the U.S., diabetes mellitus is both serious and costly. The 2001 estimate is that 7.9% of the population (16.7 million people) in the U.S. had been diagnosed with diabetes[2] with perhaps another 6 million not yet diagnosed. Many people also have other abnormalities of glucose (sometimes called "prediabetes") manifest either as impaired fasting glucose (IFG) levels or as impaired glucose tolerance (IGT). The criteria for diagnosis of diabetes and prediabetes are summarized in Table 1.[3] Collectively, diabetes, IFG, and IGT have been dubbed "dysglycemia".[4] The combination of dysglycemia, obesity, dyslipidemia, and blood pressure elevation is known as the "metabolic syndrome" or the "dysmetabolic syndrome" or "diabesity". A number of metabolic and clinical abnormalities are included in the dysmetabolic syndrome, as summarized in Table 2. Among American adults, the age-adjusted prevalence of metabolic syndrome is 23.7% overall and over 40% in individuals over age 60.[5] Obesity itself, defined as a body mass index (BMI) of ≥30 kg/m$^2$, is present in 20.9% of the U.S. population, or an estimated 44.3 million people.[2] Given the double problem of increasing rates of obesity and the trend toward more sedentary lifestyles, diabetes is one of our most serious epidemics.[6] Diabetes mellitus is also an enormous economic burden in the U.S. In 2002, $132 billion was spent on diabetes.[7] Per capita expenditure by people with diabetes is 2.4 times that spent by the nondiabetic population (adjusted for age, gender, and ethnicity).[7] The burden of diabetes (in terms of risk of complications and impact on morbidity and mortality) is enormous.[8]

The human burden of diabetes is a consequence of the devastating chronic complications of the disease. In the U.S., diabetes remains the leading cause of new blindness in adults, with 24 000 individuals becoming legally blind every year because of diabetes.[9] Diabetes now accounts for 43% of patients entering dialysis or transplantation, making it by far the leading cause of end-stage renal disease.[10] Compared to the nondiabetic population, people with diabetes are 2- to 6-fold more likely to have heart disease and 2- to 4-fold more likely to have a stroke.[11] Diabetes results in a 15- to 40-fold increased risk of amputations compared to nondiabetic population and thus is the nation's leading cause of nontraumatic lower limb amputations, accounting for 60% of all such amputations.[11] Each year, an estimated 82 000 limbs are lost because of diabetes.

**Table 1.** Diagnostic Criteria for Diabetes Mellitus and Prediabetes[a]

| | fasting[b] plasma glucose mg/dL (mmol/L) | | 2 h[c] plasma glucose mg/dL (mmol/L) |
|---|---|---|---|
| normal | <100 (5.6) | | < 140 (7.8) |
| prediabetes | | | |
| impaired fasting glucose | 100−125 (5.6−6.9) | | |
| impaired glucose tolerance | | | 140−199 (7.8−11.0) |
| diabetes mellitus | ≥126 (7.0) | or | ≥200 (11.1) |

[a] Diabetes also may be diagnosed with plasma glucose greater than 200 mg/dL (11.1 mmol/L) and unequivocal symptoms (polyuria, polydipsia, unexplained weight loss). Diagnostic criteria for diabetes mellitus includes confirmation on a subsequent day. [b] Fasting = no caloric intake for at least 8 h. [c] 2 h following a 75 g oral glucose load, i.e., oral glucose tolerance test (OGTT).

**Table 2.** Components of the Dysmetabolic Syndrome

- insulin resistance—hyperinsulinemia relative to glucose levels
- acanthosis nigricans
- central obesity
- glucose intolerance or type 2 diabetes
- blood pressure elevation or hypertension
- dyslipidemia—hypertriglyceridemia and decreased HDL cholesterol, small, dense LDL cholesterol particles
- increased plasma uric acid
- hypercoagulability—increased plasminogen activator inhibitor
- vascular endothelial dysfunction
- coronary artery disease

In terms of the impact on these complications, randomized controlled clinical trials, completed over the past decade, have clearly and unambiguously demonstrated the benefits in diabetic patients of meticulous glycemic control,[12−14] aggressive blood pressure control,[15−17] lowering of LDL cholesterol,[18−20] and use of aspirin therapy.[21−23] There can no longer be any excuse to ignore these important risk factors.

## Pathophysiology of Diabetes

Diabetes mellitus actually is a group of metabolic diseases characterized by hyperglycemia arising as a consequence of a relative or absolute deficiency of insulin secretion, resistance to insulin action, or both.[24,25]

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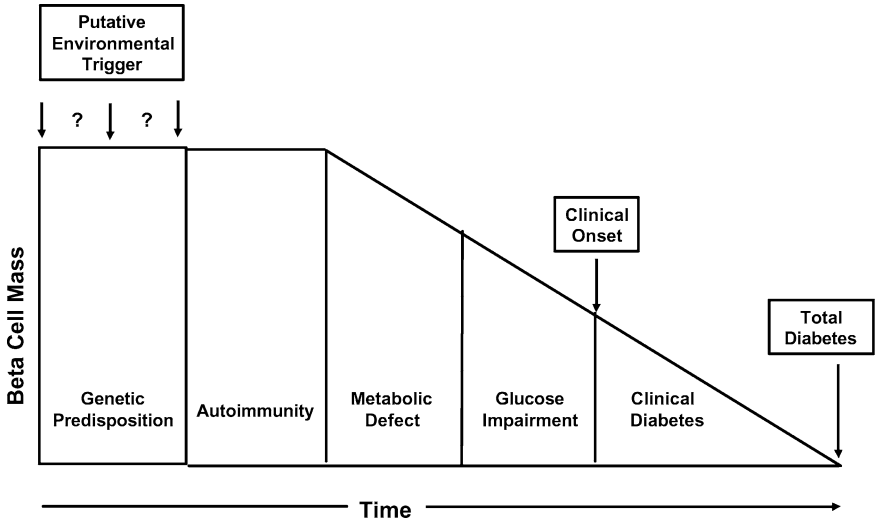


**Figure 1.** Schematic representation of the slow, progressive loss of $\beta$-cell mass during the development of type 1 diabetes. The disease process includes genetic predisposition, autoimmunity (recognizable by autoantibodies), a metabolic defect with progressive loss of insulin secretion, "pre"-diabetes, and overt diabetes.

Although diabetes mellitus is recognized by its characteristic hyperglycemia, the metabolic derangements are more pervasive, involving altered metabolism of carbohydrates, fats, and proteins. As a function of time and consequent to the metabolic disruption, diabetic patients may suffer the tragic ravages of long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels, as noted above.

Although several pathogenic processes may be involved in the development of diabetes, the vast majority of cases fall into two main categories: type 1 diabetes and type 2 diabetes. Type 1 diabetes is usually due to an immune-mediated destruction of pancreatic islet $\beta$-cells with consequent insulin deficiency and the need to replace insulin.[26] Although usually having an abrupt clinical onset, the disease process unfolds slowly, with progressive loss of $\beta$-cells, as depicted in Figure 1. Type 1 diabetes is a consequence of significant loss of $\beta$-cell mass and/or function and invariably requires therapeutic replacement of insulin. Type 2 diabetes, the more common type, is usually due to resistance to insulin action in the setting of inadequate compensatory insulin secretory response.[24,25] This is depicted in Figure 2. Insulin resistance is actually quite common because it arises as a consequence of obesity, a sedentary lifestyle, and aging (Figure 3), with resulting hyperglycemia and diabetes, blood pressure elevation, and dyslipidemia. In fact, collectively these abnormalities, which often occur together, have been designated the "metabolic syndrome" or more properly the "dysmetabolic syndrome" (Table 1). Type 2 diabetes does not emerge in all persons with insulin resistance but rather only in those with a defect in insulin secretory capacity (presumably genetic) such that pancreatic insulin secretion fails to compensate for the insulin resistance (Figure 2). The initial manifestation of the insulin secretory abnormality is a loss of "first-phase" insulin secretion, as depicted in Figure 4. Ultimately, however, even in type 2 diabetes, there is a progressive loss of pancreatic islet $\beta$-cells resulting in insulin deficiency and the need to replace insulin.[27]

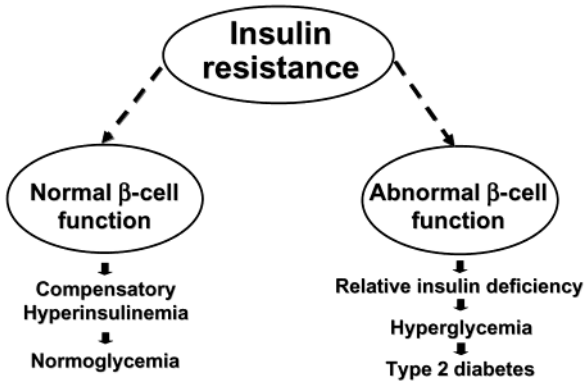


**Figure 2.** Schematic depiction of the dual defect that is necessary for type 2 diabetes to be manifest: insulin resistance in the setting of impaired $\beta$-cell function inadequate to compensate for the insulin resistance.

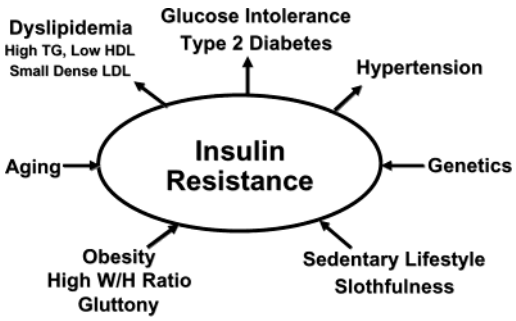


**Figure 3.** Causes and consequences of insulin resistance. Insulin resistance arises from obesity (particularly central obesity), a sedentary lifestyle, and aging (perhaps related to progressive loss of muscle mass or sarcopenia) and may have a genetic proclivity to occurrence in some individuals. Potential consequences of insulin resistance include hyperglycemia and type 2 diabetes, blood pressure elevation (potentially leading to hypertension in those with a genetic risk of essential hypertension), and a dyslipidemia characterized by elevated triglycerides, low HDL cholesterol, and small, dense LDL cholesterol (an atherogenic lipid pattern).

The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues, resulting from inadequate

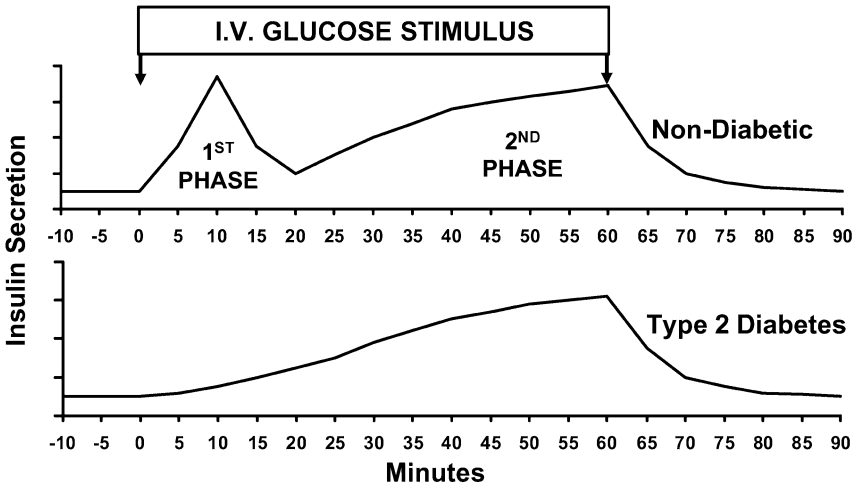


**Figure 4.** Patterns of insulin secretory response to a continuous intravenous glucose infusion, illustrating the normal biphasic response (top) and a response typical of type 2 diabetes (bottom).

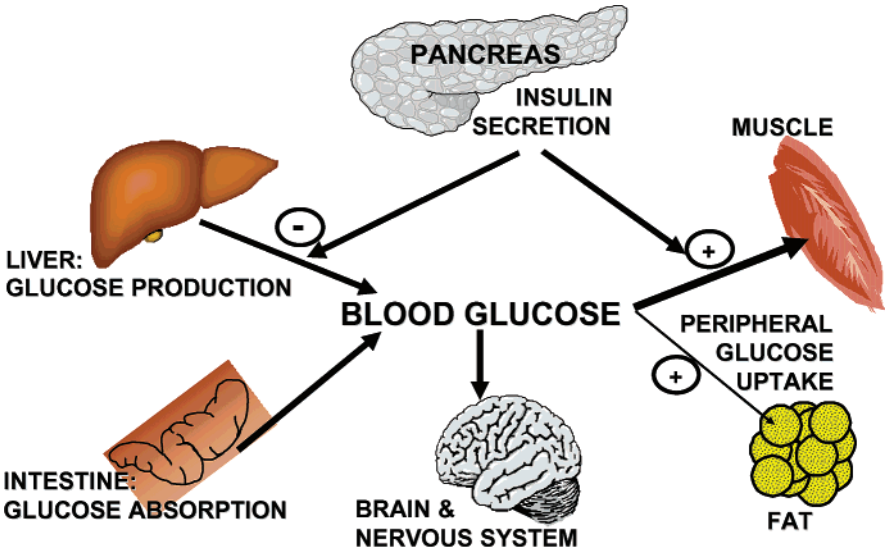


**Figure 5.** Scheme of regulation of blood glucose. Glucose input is from food intake via the gastrointestinal tract or during the basal state from hepatic glucose production, which is modulated by basal insulin secretion. The brain and nervous tissue use glucose independent of insulin, while insulin stimulates glucose uptake and utilization by peripheral tissues (here represented by muscle and adipose tissue).

insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. At a macroscopic level, one can conceptually divide the day into two basic time periods: the basal or fasting state (overnight and between meals) and the prandial state (after consuming meals). Hyperglycemia occurs in the basal or fasting state because of increased hepatic glucose production, which is a consequence of both an insulin secretory abnormality (lack of first-phase insulin secretion) and hepatic resistance to insulin, the net result being inadequate modulation by insulin of the hepatic glucose production.[24,25] In contrast, hyperglycemia in the prandial state arises because of increased absorption of glucose from the gastrointestinal track and decreased ability to dispose of the consumed glucose load, due to inadequate insulin secretion to compensate for resistance to insulin action in tissues where glucose is disposed, principally muscle and adipose tissue.[24,25] Figure 5 depicts the scheme of regulation of blood glucose and provides a number of potential targets for therapeutically regulating blood glucose.

## Treatment Approaches

The cornerstone of treatment of diabetes is lifestyle modification through increased physical activity and attention to food intake, particularly among the obese in whom weight loss is the principal goal. When lifestyle modifications do not result in normalization or near-normalization of metabolic abnormalities, pharmacologic therapy is required. Before 1995 in the U.S., sulfonylureas were the only oral antidiabetic agents available for the treatment of type 2 diabetes. More than 50% of patients were treated with oral monotherapy, 40% of patients were treated with insulin therapy, and a small percentage of patients were using sulfonylureas in combination with insulin. Since 1995, there has been an explosion of introductions of new classes of pharmacologic agents.[28−30] Currently available oral antidiabetic agents are listed in Table 3. The classes currently available include insulins and insulin analogues,[31−33] sulfonylureas,[34] glinides,[30] biguanides,[35−36] glitazones (thiazolidinediones),[37] and α-glucosidase inhibitors.[38] More recently, combination products have been intro-

**Table 3.** Oral Antidiabetic Agents Available in the U.S.

| generic name | brand name |
|---|---|
| **Sulfonylureas** | |
| tolbutamide | Orinase |
| chlorpropamide | Diabinese |
| tolazamide | Tolinase |
| acetohexamide | Dymelor |
| glipizide | Glucotrol |
| glipizide-gits | Glucotrol-XL |
| glyburide | Diabeta, Micronase |
| glyburide (micronized) | Glynase |
| glimiperide | Amaryl |
| **Glinides (Meglitinides)** | |
| repaglinide | Prandin |
| nateglinide | Starlix |
| **Biguanides** | |
| metformin | Glucophage |
| metformin-XR | Glucophage-XR |
| **Glitazones (Thiazolidinediones)** | |
| rosiglitazone | Avandia |
| pioglitazone | Actos |
| **α-Glucoside Inhibitors** | |
| acarbose | Precose |
| miglitol | Glyset |
| **Combination Therapies** | |
| glyburide−metformn | Glucovance |
| glipizide−metformin | Metaglip |
| rosiglitazone−metformin | Avandamet |

**Table 4.** Insulin Preparations Available in the U.S. or Pending Regulatory Approval[a]

| generic name | brand name |
|---|---|
| **Short-Acting Preparations** | |
| regular insulin (animal) | Iletin-R, Novo-R |
| regular human insulin | Humulin-R, Novolin-R |
| buffered regular insuin | Velosulin |
| insulin lispro | Humalog |
| insulin aspart | Novolog |
| insulin glulisine | Apidra |
| **Intermediate-Acting Preparations** | |
| NPH insulin (animal) | Iletin-N, Novo-N |
| NPH human insulin | Humulin-N, Novolin-N |
| lente insulin (animal) | Iletin-L |
| lente human insulin | Humulin-L |
| **Long-Acting Preparations** | |
| ultralente human insulin | Humulin-U |
| insulin glargine | Lantus |
| insulin detemir | Levemir[a] |
| **Premixed Preparations** | |
| 70% NPH/30% regular | Humulin 70/30, Novolin 70/30 |
| 50% NPH/50% regular | Humulin 50/50 |
| 75% intermediate/25% lispro | Humalog 75/25 |
| 70% intermediate/30% aspart | Novolog 70/30 |

[a] Pending regulatory approval.

duced as well. Additional insulin preparations, including insulin analogues, have also been introduced into the market over the past decade. Currently available insulins and insulin analogues are listed in Table 4. Pending regulatory approval is pramlintide, an amylin analogue that further lowers glycemia in insulin treated type 1 and type 2 diabetes.[39,40]

**Table 6.** Principal Limiting Factors in the Use of Currently Available Classes of Agents for Treatment of Diabetes Mellitus

| | hypoglycemia | weight gain | other |
|---|---|---|---|
| insulin or insulin analogues | √ | √ | injections |
| sulfonylureas | √ | √ | |
| glinides | √ | √ | |
| biguanides | no | no | lactate production |
| glitazones | no | √√ | fluid retention |
| α-glucosidase inhibitors | no | no | GI side effects |

Each of the classes of drugs has effects on one or more of the major pathways of glucose regulation depicted in Figure 5. The major pathways impacted by each class are listed in Table 5. The limiting factors for each class are listed in Table 6.

The usual treatment strategy in type 2 diabetes (when lifestyle changes are insufficient to achieve acceptable glycemic control) is to start with either metformin or a secretagogue. If adequate control is still not achieved, the second step is to add a complementary drug, i.e., one working by a different pathway. The most common such combination is metformin plus a secretagogue. If adequate glycemic control is still not attained, the choices are the following: add a third class of oral drugs (e.g., glitazone or glucosidase inhibitor), add an intermediate or long acting basal insulin, switch to insulin, or consult a diabetes specialist team. An increasing practice if the patient is switched to insulin is later to consider adding an insulin sensitizer, i.e., either metformin or a glitazone. If basal insulin alone was used, the next step is to switch to a multiple-component insulin program. Finally, once on insulin, if adequate glycemic control is still not attained, a future option is to add pramlintide.

Because of the natural progression of type 2 diabetes, most people with diabetes eventually require therapy with insulin. Yet with the progressive nature of type 2 diabetes, there is a real need for newer pharmacologic approaches aimed at additional treatment targets. The companion papers address several areas of intense research interest.

## Conclusion

There is a pressing need for improvement in diabetes care. The prevalence of diabetes is increasing at an alarming rate, and diabetes mellitus is presenting an enormous economic burden in terms of direct health care expenditures and costs of treating diabetic complications. Although there are a number of relatively new classes of therapeutic agents, none is optimal and none alone (save insulin or insulin analogues) achieves satisfactory glycemic control that can be sustained.

**Table 5.** Principal Glucose-Lowering Actions of Currently Available Classes of Agents for Treatment of Diabetes Mellitus

| | correct insulin deficiency | stimulate insulin secretion | decrease hepatic glucose production | increase muscle glucose utilization | retard carbohydrate absorption |
|---|---|---|---|---|---|
| insulin or insulin analogues | X | | | | |
| sulfonylureas | | X | | | |
| glinides | | X | | | |
| biguanides | | | X | (X) | |
| glitazones | | | (X) | X | |
| α-glucosidase inhibitors | | | | | X |

Thus, combinations of complementary agents play an ever increasing role in the treatment of the disease. Moreover, the development of newer agents aimed at additional targets should enhance our ability to effectively treat this important disease.

## Biography

**Jay S. Skyler**, M.D., is Professor of Medicine, Pediatrics, and Psychology at the University of Miami, Miami, FL, where he is Director of the Division of Endocrinology, Diabetes, and Metabolism in the Department of Medicne; Associate Director for Academic Programs in the Diabetes Research Institute; and Program Director of the General Clinical Research Center. He is Chairman of the NIH sponsored Type 1 Diabetes TrialNet, a nationwide network that conducts clinical trials to prevent type 1 diabetes or interdict the type 1 diabetes disease process. He is a past President of the American Diabetes Association, the International Diabetes Immunotherapy Group, and the Southern Society for Clinical Investigation and was a Vice-President of the International Diabetes Federation. He was the founding Editor-in-Chief of *Diabetes Care*.

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