Type 2 Diabetes Mellitus: Update on Diagnosis, Pathophysiology, and Treatment

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Sixteen million individuals in the United States with type 2 diabetes mellitus and an additional 30–40 million with impaired glucose tolerance result in health care costs exceeding 100 billion dollars annually (1). Treatment is predominantly directed at microvascular and macrovascular complications (2). In type 1 diabetes mellitus the relationship between glycemic control and microvascular complications has been well established (3). The relationship between tight glycemic control and microvascular disease in type 2 diabetes mellitus appears to be established in the recently completed United Kingdom prospective diabetes study (4, 5).

Despite the morbidity and mortality associated with retinopathy, nephropathy, and neuropathy, cardiovascular disease remains the leading cause of death in type 2 diabetes mellitus (6, 7). Consequently, the treatment of confounding risk factors of obesity, hypertension, and hyperlipidemia assumes major importance and must be coordinated with good glycemic control for reduction in total mortality in type 2 diabetes mellitus (6–11).

Based on the emerging relationship between the degree of glycemic control and microvascular complications as well as the contribution of hyperglycemia in the development of macrovascular disease, it is the purpose of this review to summarize the current state of knowledge to provide a rational basis for the treatment of type 2 diabetes mellitus.

Classification of type 2 diabetes mellitus

The definition of type 2 diabetes mellitus, previously termed noninsulin-dependent diabetes mellitus, was recently modified by the American Diabetes Association. Several criteria may be used independently to establish the diagnosis: 1) a 75-g oral glucose tolerance test with a 2-h value of 200 mg/dL or more, 2) a random plasma glucose of 200 mg/dL or more with typical symptoms of diabetes, or 3) a fasting plasma glucose of 126 mg/dL or more on one occasion (7). Fasting glucose values are preferred for their convenience, reproducibility, and correlation with increased risk of microvascular complications.

The term impaired fasting glucose has been defined as fasting plasma glucose of 110 or more and 125 mg/dL or less (7). Impaired glucose tolerance (IGT) is defined as a 2-h plasma glucose value of 140 or more and of less than 200 mg/dL during an oral glucose tolerance (12).

Individuals with impaired fasting glucose and IGT are considered to be at high risk for the development of diabetes and macrovascular disease (13, 14). Although one third of these patients will eventually develop diabetes, dietary modification and exercise can lower the risk of progression from impaired glucose tolerance to type 2 diabetes; and may also prevent the development of IGT in nondiabetic individuals at high risk (14). Pharmacological agents may also be of benefit in limiting the progression from IGT to diabetes (13, 15).

Pathophysiology of type 2 diabetes mellitus

Type 2 diabetes mellitus is a heterogeneous disorder with varying prevalence among different ethnic groups. In the United States the populations most affected are native Americans, particularly in the desert Southwest, Hispanic-Americans, and Asian-Americans (1). The pathophysiology of type 2 diabetes mellitus is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function, eventually leading to β-cell failure.

The primary events are believed to be an initial deficit in insulin secretion and, in many patients, relative insulin deficiency in association with peripheral insulin resistance (16, 17).

The β-cell

β-Cell dysfunction is initially characterized by an impairment in the first phase of insulin secretion during glucose stimulation and may antedate the onset of glucose intolerance in type 2 diabetes (18).

Initiation of the insulin response depends upon the transmembranous transport of glucose and coupling of glucose to the glucose sensor. The glucose/glucose sensor complex then induces an increase in glucokinase by stabilizing the protein and impairing its degradation. The induction of glucokinase serves as the first step in linking intermediary metabolism with the insulin secretory apparatus. Glucose transport in β-cells of type 2 diabetes patients appears to be greatly reduced, thus shifting the control point for insulin secretion from glucokinase to the glucose transport system (19, 20). This defect is improved by the sulfonylureas (21, 22).

Later in the course of the disease, the second phase release...
of newly synthesized insulin is impaired, an effect that can be reversed, in part at least in some patients, by restoring strict control of glycemia. This secondary phenomenon, termed desensitization or β-cell glucotoxicity, is the result of a paradoxical inhibitory effect of glucose upon insulin release and may be attributable to the accumulation of glycogen within the β-cell as a result of sustained hyperglycemia (23). Other candidates that have been proposed are sorbital accumulation in the β-cell or the nonenzymatic glycation of β-cell proteins.

Other defects in β-cell function in type 2 diabetes mellitus include defective glucose potentiation in response to non-glucose insulin secretagogues, asynchronous insulin release, and a decreased conversion of proinsulin to insulin (24, 25).

An impairment in first phase insulin secretion may serve as a marker of risk for type 2 diabetes mellitus in family members of individuals with type 2 diabetes mellitus (26–30) and may be seen in patients with prior gestational diabetes (31). However, impaired first phase insulin secretion alone will not cause impaired glucose tolerance.

Autoimmune destruction of pancreatic β-cells may be a factor in a small subset of type 2 diabetic patients and has been termed the syndrome of latent autoimmune diabetes in adults. This group may represent as many as 10% of Scandinavian patients with type 2 diabetes and has been identified in the recent United Kingdom study, but has not been well characterized in other populations (4–6).

Glucokinase is absent within the β-cell in some families with maturity-onset diabetes of young (31). However, deficiencies of glucokinase have not been found in other forms of type 2 diabetes (32, 33).

In summary, the delay in the first phase of insulin secretion, although of some diagnostic import, does not appear to act independently in the pathogenesis of type 2 diabetes. In some early-onset patients with type 2 diabetes (perhaps as many as 20%) (4, 5), there may be a deficiency in insulin secretion that may or may not be due to autoimmune destruction of the β-cell and is not due to a deficiency in the glucokinase gene. In the great majority of patients with type 2 diabetes (±80%), the delay in immediate insulin response is accompanied by a secondary hypersecretory phase of insulin release as a result of either an inherited or acquired defect within the β-cell or a compensatory response to peripheral insulin resistance. Over a prolonged period of time, perhaps years, insulin secretion gradually declines, possibly as a result of intrasilet accumulation of glucose intermediary metabolites (34). In view of the decline in β-cell mass, sulfonylureas appear to serve a diminishing role in the long term management of type 2 diabetes (35). Unanswered is whether amelioration of insulin resistance with earlier detection or newer insulin-sensitizing drugs will retard the progression of β-cell failure, obviating or delaying the need for insulin therapy.

Insulin resistance

Emanating from the prismatic demonstration by Yalow and Berson of the presence of hyperinsulinism in type 2 diabetes, insulin resistance has been considered to play an integral role in the pathogenesis of the disease (36). Recent critical reviews, however, have questioned the primacy, specificity, and contribution of insulin resistance to the disease state (37, 38). As chronic hyperinsulinemia inhibits both insulin secretion (39) and action (40), and hyperglycemia can impair both the insulin secretory response to glucose (41) as well as cellular insulin sensitivity (42, 43), the precise relation between glucose and insulin level as a surrogate measure of insulin resistance has been questioned. Lean type 2 diabetic patients over 65 yr of age have been found to be as insulin sensitive as their age-matched nondiabetic controls (44). Moreover, in the majority of type 2 diabetic patients who are insulin resistant, obesity is almost invariably present (45, 46). As obesity or an increase in intraabdominal adipose tissue is associated with insulin resistance in the absence of diabetes, it is believed by some that insulin resistance in type 2 diabetes is entirely due to the coexistence of increased adiposity (47). Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease, entities commonly found in association with diabetes (16, 48, 49), again raising the question as to whether insulin resistance results from different pathogenetic disease processes or is unique to the presence of type 2 diabetes (16, 50, 51).

Prospective studies have demonstrated the presence of either insulin deficiency or insulin resistance before the onset of type 2 diabetes (48). Two studies have reported the presence of insulin resistance in nondiabetic relatives of diabetic patients at a time when their glucose tolerance was still normal (52, 53). In addition, first degree relatives of patients with type 2 diabetes have been found to have impaired insulin action upon skeletal muscle glycogen synthesis due to both decreased stimulation of tyrosine kinase activity of the insulin receptor and reduced glycogen synthase activity (54, 55). Other studies in this high risk group have failed to demonstrate insulin resistance, and in the same group, impaired early phase insulin release and loss of normal oscillatory pattern of insulin release have been described (56, 57). Based upon these divergent studies, it is still impossible to dissociate insulin resistance from insulin deficiency in the pathogenesis of type 2 diabetes. However, both entities unequivocally contribute to the fully established disease.

The liver

The ability of insulin to suppress hepatic glucose production both in the fasting state and postprandially is normal in first degree relatives of type 2 diabetic patients (26). It is the increase in the rate of postprandial glucose production that heralds the evolution of IGT (52). Eventually, both fasting and postprandial glucose production increase as type 2 diabetes progresses. Hepatic insulin resistance is characterized by a marked decrease in glucokinase activity and a catalytic increased conversion of substrates to glucose despite the presence of insulin (53). Thus, the liver in type 2 diabetes is programmed to both overproduce and underuse glucose. The elevated free fatty acid levels found in type 2 diabetes may also play a role in increased hepatic glucose production (50). In addition, recent evidence suggests an important role for the kidney in glucose production via gluconeogenesis, which is unrestrained in the presence of type 2 diabetes (58).
**Therapy for type 2 diabetes mellitus**

**Diet.** Diet therapy, although important for the prevention as well as the treatment of all stages of type 2 diabetes, continues to remain poorly understood and high controversial (59, 60). When obesity coexists with hyperglycemia, as seen in the majority of individuals with type 2 diabetes, weight reduction is the major goal of dietary therapy (61–64). Traditional recommendations emphasize reduction of both the total and saturated fat content and replacement with complex carbohydrates to 50–55% of the dietary calories. In type 2 diabetic patients, such diets may cause marked postprandial hyperglycemia. As there is considerable patient variability in the rate of glucose absorption, arduous attention to postprandial glucose monitoring and the addition of high fiber contents to the diet become critically important. Moreover, as the glycemic response of the diet is also dependent upon the texture and content of other food stuffs in the diet as well as the rate of intestinal motility, the diet as well as the stage and duration of type 2 diabetes have to be considered on an individual basis (59, 65, 66).

**Exercise.** Exercise has been shown to be beneficial in the prevention of the onset of type 2 diabetes mellitus as well as in the improvement of glucose control as a result of enhanced insulin sensitivity (67–70). Decreased intraabdominal fat, an increase in insulin-sensitive glucose transporters (GLUT-4) in muscle, enhanced blood flow to insulin-sensitive tissues, and reduced free fatty acid levels appear to be the mechanisms by which exercise restores insulin sensitivity (71). In addition, exercise provides the added benefits of lowering blood pressure, improving myocardial performance, and lowering serum triglycerides while raising high density lipoprotein cholesterol levels.

**Pharmacotherapy therapy for type 2 diabetes mellitus**

Current therapeutic agents available for type 2 diabetes mellitus include sulfonylureas and related compounds, biguanides, thiazolidinediones, α-glucosidase inhibitors and insulin (Table 1). In addition, several other classes of therapeutic agents will soon become available. A rational approach would be to begin with the agents particularly suited to the stage and nature of the disease, progressing, if necessary, to combination therapy. Pharmacological agents acting through different mechanisms of action should be chosen to improve glucose values while minimizing adverse effects.

**Sulfonylureas and related agents.** Sulfonylureas have been used to treat type 2 diabetes since 1942 and require functional β-cells for their hypoglycemic effect (22, 73). All currently available sulfonylureas bind to specific receptors on β-cells, resulting in closure of potassium ATP channels. As a result, glucose channels open, leading to an increase in cytoplasmic calcium that stimulates insulin release (74). A newer sulfonylurea, glipizide, given in doses of 1, 4, or 8 mg preprandially, appears to have a more rapid onset than previous sulfonylureas (both glyburide and glipizide) and consequently less risk of hypoglycemia (75). To a lesser degree than insulin administration, sulfonylureas, through endogenous hyperinsulinemia, cause a propensity for hypoglycemia and weight gain (76). Still controversial is the influence of sulfonylureas on cardiovascular mortality, an observation first described by the University Group Diabetes Program (77). Because of the variability of baseline data and subsequent studies that failed to substantiate the observation, sulfonylureas have not been considered to potentiate cardiovascular risk in diabetic patients (78). However, newer data has shown that sulfonylureas, with the exception of glipizide, block the vasodilator response to ischemia in animals, thereby potentially increasing cardiovascular risk. At present, the question regarding sulfonylurea use in cardiovascular mortality in humans remains unanswered (79, 80). Located in the context of our increasing understanding of the pathogenesis of type 2 diabetes, sulfonylureas would be most appropriate in those patients in whom hypoinsulinemia is the predominant cause of hyperglycemia. These patients would typically be lean, with lower basal and postprandial insulin levels. In addition, based upon the recent United Kingdom study, these patients tend to be younger (<46 yr of age) and are more likely to require insulin therapy (81).

Repaglinide is a new agent that binds to pancreatic β-cells and stimulates insulin release. It is structurally different from sulfonylureas and binds to a nonsulfonylurea receptor (82). The drug is taken preprandially and has a rapid onset and limited duration of action, which may decrease the incidence of weight gain and hypoglycemic episodes. Limited published clinical data demonstrate an efficacy similar to that of sulfonylureas; as with sulfonylureas, repaglinide shows an added benefit when given with metformin (82, 83).

**Biguanides.** After withdrawal of the biguanide, phenformin, from the U.S. market in 1975, a second generation biguanide, metformin, was introduced and widely distributed throughout Western Europe, Canada, and Mexico. With a frequency of lactic acidosis 1/10th that of the parent compound and a strong record of safety and efficacy, the drug was carefully introduced into the American market in 1995.

Glucose lowering by the drug occurs primarily by decreasing hepatic glucose production and, to lesser extent, by decreasing peripheral insulin resistance. The drug acts by causing the translocation of glucose transporters from the plasma membranes of liver and muscle to the periphery, resulting in a decrease in hepatic glucose output and a redistribution of glucose uptake in the periphery.

### TABLE 1. Oral agents used in the management of type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of action</th>
<th>Indication(s)</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylureas and repaglinide</td>
<td>Increase insulin secretion</td>
<td>Insulinopenia</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Decrease hepatic gluoneogenesis</td>
<td>Obesity + insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Decrease peripheral insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Decrease peripheral insulin resistance</td>
<td>Insulin resistance</td>
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<tr>
<td></td>
<td>Reduce fatty acids</td>
<td></td>
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<tr>
<td>α-glucosidase inhibitors</td>
<td>Slow absorption of carbohydrates</td>
<td>Postprandial hyperglycemia</td>
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microsomal fraction to the plasma membrane of hepatic and muscle cells. It does not stimulate insulin release and does not, when given alone, cause hypoglycemia (84). Moreover, it does not cause weight gain, and it improves the lipid profile by causing a decline in total and very low density lipoprotein triglyceride, total cholesterol, and very low density cholesterol levels and an increase in high density lipoprotein cholesterol levels (85–90). It is ideally suited for obese patients with type 2 diabetes who are unresponsive to diet alone and are presumed to be insulin resistant.

When introduced gradually in 500- or 850-mg increments to a maximum dose of 2000 mg daily, a reduction in hemoglobin A1c (HbA1c) up to 2.0% (60 mg/dL decrement in average glucose level) can be anticipated. It is effective as monotherapy or in combination with other agents, such as insulin secretagogues, other insulin-sensitizing drugs, or inhibitors of glucose absorption.

The major risk continues to be that of lactic acidosis, which occurs with a frequency of 1/20,000 patient yr. As the major route of excretion of the drug is through the kidneys, it should not be given to those with renal disease (creatinine ≥1.5 in males; ≥1.4 in females), in the presence of hepatic disease, or in patients with tissue ischemia. In addition, the drug should be withheld for 48 h after iv contrast administration (91).

**Thiazolidenediones**

This new class of antidiabetic agents has been under investigation since 1983 (92). To date, the only drug brought to market is troglitazone, although companion drugs, including Pioglitazone, englitazone, and BRL 49653 are under active investigation (93). Troglitazone differs from other thiazolidenediones in that it contains an α-tocopherol moiety as part of its structure, which may also provide some antioxidant properties (94).

Thiazolidenediones appear to act by binding to the peroxisome proliferator activator receptor-γ (95, 96). This nuclear receptor influences the differentiation of fibroblasts into adipocytes and lowers free fatty acid levels (95). Clinically, its major effect is to decrease peripheral insulin resistance, although at higher doses it may also decrease hepatic glucose production (15, 97). Although acting at a different site than metformin, both troglitazone and metformin appear to function as insulin sensitizers and require the presence of insulin for their effects (98, 99). In contrast to metformin, the effects of troglitazone may be progressive over time, and its full hypoglycemic potency may not be achieved until 12 weeks of therapy (100). When given in doses of 200–600 mg daily, a maximum decrement in HbA1c of 1.5% (45 mg/dL) may be anticipated when the drug is given alone. Whereas metformin generally improves glycemic control in greater than 90% of patients, a response to troglitazone is generally seen in approximately 60% of patients (98). An elevated C peptide level may help to predict a beneficial response of either drug, and as metformin and troglitazone act at different sites to restore insulin sensitivity, further improvement is seen when the two drugs are used in combination (101). Moreover, as insulin resistance is invariably accompanied by a relative insulin deficiency, either metformin or troglitazone will be further benefited when either or both drugs are given along with an insulin secretagogue. Troglitazone may cause peripheral edema or dilutional anemia, limiting its use in renal disease. However, the major concern of the drug is that of hepatotoxicity. Occurring in 2% of patients, it has been reported as early as 35 days and as late as 8 months after the onset of therapy. Therefore, measurement of transaminases and bilirubin monthly for the first 8 months of therapy and every 2 months thereafter for the first year of therapy is mandatory. Early detection has invariably led to reversal of hepatotoxicity (102, 103).

**α-Glucosidase inhibitors**

Members of this class act by slowing the absorption of carbohydrates from the intestines and thereby minimize the postprandial rise in blood glucose (104). Gastrointestinal side-effects require gradual dosage increments over weeks to months after therapy is initiated. Serious adverse reactions are rare, and weight gain may be minimized with this therapy. Acarbose, the agent of this class in clinical use, may be added to most other available therapies (105).

**Insulin**

Insulin therapy is indicated in the treatment of type 2 diabetes for initial therapy of severe hyperglycemia, after failure of oral agents, or during perioperative or other acute hyperglycemic states. Insulin has been used in multiple combinations in type 2 diabetes, and new insulin analogs are in clinical trials (106). The first available insulin analog is lispro insulin, representing a two-amino acid modification of regular human insulin. Lispro insulin does not form aggregates when injected sc, allowing it to have a more rapid onset and a shorter duration of action than regular insulin (107). Although these properties may help minimize the postprandial rise in glucose and decrease the risk of late hypoglycemia (108), the use of insulin in type 2 diabetes is not without theoretical as well as practical concerns. Insulin therapy can cause further weight gain in obese type 2 diabetics and increase the risk of hypoglycemia (although less commonly than in type 1 diabetes) (109). In addition, the peripheral hyperinsulinemia achieved by exogenous insulin therapy may be a risk factor for cardiovascular disease (110–112).

**Combination therapies**

Most available agents have been used in combination to treat type 2 diabetes. Although many combinations are not yet approved for use, a rational choice for combination therapy would include an agent that increases insulin levels and one that enhances sensitivity to insulin and lowers glucose production. This combination of agents would appear to correct most of the pathophysiological defects found in type 2 diabetic individuals.

**Investigational therapies**

It is well established that an oral glucose load evokes a greater insulin response than glucose given by the iv route (113). One of the gut polypeptides responsible for this observation is glucagon-like peptide (GLP-1) (114). Given par-
enterally or through the buccal mucosa, GLP-1 lowers glucose levels, decreases glucagon levels, and delays gastric emptying (115–117). Its role as an adjunctive treatment of type 2 diabetes is currently under investigation. Caution in its application will be necessary in those patients with gastroparesis.

Amylin is a β-cell peptide cosecreted along with insulin. Found to be absent or markedly reduced in type 1 diabetes (118), its presence in type 2 diabetes varies with the state of β-cell function. When given parenterally, it appears to decrease the glucagon level and delay gastric emptying, thereby facilitating insulin action (119, 120). It, too, will require caution in its use in patients with gastroparesis.

Insulin-like growth factor I (IGF-I) levels decline with aging in parallel with the decline in insulin sensitivity (121). Although a cause and effect relationship has not been established, the administration of IGF-I can cause a modest improvement in insulin sensitivity (121). Its potential benefit must be balanced with the requirement for parenteral administration, expense, and theoretical potential to worsen vascular complications, particularly retinopathy (122). Because of these concerns, IGF-I trials have been temporarily discontinued.

**Therapeutic paradigm and conclusions**

Any approach to treatment of type 2 diabetes must combine education, diet, exercise, and management of multiple risk factors. Control of hypertension and dyslipidemia is essential. Blood pressure of less than 130/85 mm Hg and a low density lipoprotein cholesterol level below 130 mg/dL (low density lipoprotein cholesterol <100 mg/dL if coronary artery disease is present) are a suggested standard of care (123). The degree of glycemic control recommended will vary depending upon age, education, and complicating risk factors. In otherwise healthy individuals, near normalization of the glycosylated hemoglobin level is recommended (124), and in all cases a HbA1c level above 8.0% demands therapeutic intervention. In those patients in whom insulinopenia is the likely cause of hyperglycemia manifested by lean body weight, younger age, and enhanced insulin sensitivity, a sulfonylurea or another β-cell secretagogue would be favored, whereas those patients who are likely to be insulin resistant with coexistent features of hypertension, hyperlipidemia, and obesity would more likely respond to an insulin-sensitizing agent, either metformin or troglitazone. If HbA1c values continue to exceed 8%, a second agent may be added, either a secretagogue or another insulin-sensitizing agent depending upon patient characteristics, and if postprandial hyperglycemia persists, an α-glucosidase inhibitor may be added. Ultimately, insulin therapy may become necessary either early in the course of the disease to establish control or later in the disease course as β-cell failure ensues (2). The addition of bedtime insulin to sulfonylureas may offer some interim protection, and preliminary studies with insulin and the insulin-sensitizing drugs have shown promising results in delaying β-cell failure (99). Whether such combinations will provide long term benefit remains to be determined.

In just a few years in the United States, pharmacotherapy for hyperglycemia has greatly expanded, allowing many patients whose diabetes was formerly treated by insulin alone to be controlled with oral agents. However, much remains to be learned. New therapies will continue to evolve as insight into molecular mechanisms further expand our therapeutic horizon. However, we must now actively try to diagnose all type 2 diabetic individuals at an earlier stage and begin treatment in an attempt to minimize the burden of diabetes-associated complications. Diabetologists and endocrinologists will play an essential part in this goal.

**References**


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