Review

Glycemic Control, Mealtime Glucose Excursions, and Diabetic Complications in Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus is a heterogeneous disorder characterized by 2 pathogenic defects, impaired insulin secretion and insulin resistance. The resultant hyperglycemia causes microvascular and macrovascular complications that increase morbidity and mortality in patients with diabetes mellitus. Optimum glycemic control in patients with type 1 and type 2 diabetes mellitus prevents the development of microvascular disease and, to a lesser extent, macrovascular disease. Prandial hyperglycemia may be an independent risk factor for the development of diabetic complications. This article reviews the pathophysiologic mechanisms of glucose metabolism and describes the results of epidemiological and interventional studies that have demonstrated the association of acute and chronic hyperglycemia with the development of diabetic complications. The American Diabetes Association has defined diagnostic and treatment goals for diabetes mellitus, striving to achieve near-normal glycemic control to delay or prevent the development of diabetic complications. A number of oral antidiabetic agents and insulins are currently available for the treatment of type 2 diabetes mellitus in the United States. These agents target fasting and postmeal plasma glucose levels to improve glycemic control. Alone or in combination, these agents have enhanced the clinical approaches to treating diabetes mellitus.

***Mayo Clin Proc*. 2001;76:609-618**

ATP = adenosine triphosphate; CHD = coronary heart disease; DCCT = Diabetes Control and Complications Trial; DECODE = Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; FDA = Food and Drug Administration; FPG = fasting plasma glucose; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HGP = hepatic glucose production; ICAM-1 = intracellular adhesion molecule 1; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test; TRAP = total radical trapping antioxident parameter; UKPDS = United Kingdom Prospective Diabetes Study

Type 2 diabetes mellitus is a heterogeneous disorder characterized by 2 pathogenic defects, impaired insulin secretion and insulin resistance.[1-6] Impaired insulin secretion leads initially to postprandial hyperglycemia, and as beta cell function declines further, fasting hyperglycemia ensues. Insulin resistance contributes further to and aggravates the fasting and postprandial hyperglycemia. Other abnormalities associated with decreased insulin secretion and insulin resistance (hyperglycemia, hyperinsulinemia, lipolysis, hyperlipidemia, hypertension, and coagulation defects) contribute to the risk of microvascular and macrovascular disease. When data on diabetic morbidity and mortality are adjusted for the conventional risk factors of obesity, hyperlipidemia, and hypertension, individuals with diabetes mellitus exhibit an increased risk of macrovascular disease most likely related to hyperglycemia.[7]

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Dr Palumbo has received research funding from BristolMyers Squibb, Hoechst-Marion-Roussel, and Parke-Sankyo for participation in multicenter trials of drug treatment for type 2 diabetes mellitus.

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Control of hyperglycemia may markedly delay or prevent microvascular disease in patients with type 1 and type 2 diabetes mellitus but has not been shown consistently to delay or prevent macrovascular disease. Recent studies have called attention to the role of postprandial hyperglycemia as an important independent risk factor for diabetic complications.[8-10] Glycated (or glycosylated) hemoglobin (hemoglobin A_{1c} [HbA_{1c}]), which has been used as the index of glycemic control in treatment trials, represents an integration of basal and postprandial glucose levels.

This article reviews the pathophysiologic mechanisms of glucose metabolism and describes the results of epidemiological and interventional studies that have demonstrated the association of acute and chronic hyperglycemia with the development of diabetic complications. Strategies for management of type 2 diabetes mellitus based on these findings are outlined. New agents that target mealtime hyperglycemia contribute further to the management of type 2 diabetes mellitus by achieving optimum glycemic control and prevention of complications.

DIAGNOSIS AND CLASSIFICATION

Type 2 diabetes mellitus is a metabolic disorder characterized by impaired insulin secretion and insulin resistance, with hyperglycemia as the dominant feature. The Expert Committee on the Diagnosis and Classification of Diabetes

Table 1. **Criteria for the Diagnosis of Diabetes Mellitus***

Fasting plasma glucose level ≤126 mg/dL ***or***
Symptoms (polyuria, polydipsia, unexplained weight loss) plus casual plasma glucose level ≥200 mg/dL ***or***
2-h plasma glucose level ≥200 mg/dL during a 75-g oral glucose tolerance test

*Casual is defined as any time of day without regard to time of last meal. Adapted, with permission, from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[11]

Mellitus has attempted to clarify and systematize the current understanding of diabetes mellitus, its classification, and diagnosis.[11]

There are now 3 criteria by which to diagnose diabetes mellitus: (1) a patient has a fasting plasma glucose (FPG) level of 126 mg/dL or higher; (2) a symptomatic patient has a casual plasma glucose level of 200 mg/dL or higher; or (3) a patient has a 2-hour plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test (OGTT). The diagnosis must be confirmed by any of the 3 methods on a subsequent day (Table 1).[11] Based on these diagnostic criteria, an estimated 16 million people in the United States have type 2 diabetes mellitus, and about 50% of them have undiagnosed diabetes.

Considerable data from epidemiological and interventional studies have demonstrated that elevated plasma glucose levels correlate with microvascular complications, and the incidence and severity of these complications can be reduced by good glycemic control. The American Diabetes Association recommended specific goals for glycemic control (Table 2).[12] These goals now set the range for FPG levels at 80 to 120 mg/dL for people with diabetes mellitus. Normal FPG levels are defined as less than 110 mg/dL; action is recommended when FPG levels are lower than 80 mg/dL or higher than 140 mg/dL. Corresponding to these FPG levels, the normal value for glycated hemoglobin (HbA_{1c}) is defined as ranging from 4% to 6%. The recommended glycated hemoglobin level for people with diabetes mellitus is less than 7%, and action is recommended when the glycated hemoglobin level exceeds 8%. These goals of treatment may need to be modified in elderly patients (those ≥70 years old) because of potential adverse effects from the therapy in this age group.

Table 2. **American Diabetes Association Goals for Glycemic Control***

Biochemical index	Normal	Goal	Action suggested
Fasting/preprandial plasma glucose level (mg/dL)	<110	80-120	<80 or >140
Bedtime plasma glucose level (mg/dL)	<120	100-140	<100 or >160
Hemoglobin A_{1c} (%)	4-<6	<7	>8

*Adapted, with permission, from American Diabetes Association.[12]

PHYSIOLOGY AND PATHOPHYSIOLOGY

Glucose Metabolism

Normal glucose homeostasis depends on 2 states of activity—the absorptive or postmeal state and the basal or postabsorptive state. After a meal is ingested, the body's primary requirement is to maintain a normal plasma glucose level. Some but not all of this glucose maintenance is accomplished by the secretion of insulin, which occurs in 2 phases: an acute early phase and a secondary late phase. Insulin promotes cellular uptake of 25% of the glucose load into insulin-dependent tissues (mostly muscle). At the cellular level, insulin activates glucose transport and disposal pathways, with resulting storage as glycogen. Insulin and glycemia suppress hepatic glucose production (HGP), primarily by decreasing hepatic glycogenolysis. Gluconeogenesis, the other pathway by which the liver produces glucose, is suppressed by physiologic concentrations of glucose but not by insulin. The net effect in normal individuals is a greater than 95% decrease in HGP by modest increases in plasma insulin and glucose concentrations.[2,5,6,13]

The remaining 75% of the glucose load is taken up by insulin-independent tissues, brain, splanchnic organs (liver and gut), erythrocytes, and kidneys at a rate proportional to the glucose level. Adipose tissue is responsible for the disposal of less than 5% of a glucose load.[13] Plasma glucose levels are maintained at a steady state by the liver through both glycogenolysis and gluconeogenesis. The rate of HGP is matched to glucose uptake by tissues, primarily through the action of insulin. Glycogen is replaced in the liver primarily from sources such as lactate, alanine, glutamine, glycerol, or fructose and not directly from glucose.[3]

Progression of Diabetes

Beta cell dysfunction with loss of first-phase insulin secretion occurs early in patients with type 2 diabetes mellitus and results in postprandial hyperglycemia. Peripheral tissue resistance to insulin action (insulin resistance) aggravates the postprandial glycemia. As beta cell function deteriorates with decreasing second phase insulin secretion, marked hyperglycemia and hypoinsulinemia and increased fatty acid and triglyceride concentrations ensue.[4,5,8] Figure 1 shows glucose and insulin responses and tissue sensitivity to insulin during OGTT in control subjects compared with obese nondiabetic, obese glucose-intolerant, obese hyperinsulinemic diabetic, normal-weight diabetic, and obese hypoinsulinemic diabetic subjects.[2] The OGTT re-

sults remain normal as long as the insulin response increases to counteract tissue insulin resistance. In subjects with insulin resistance (plasma glucose level >200 mg/dL), progressive increases in glycemia after a glucose load are associated with decreased insulin secretion. Therefore, in type 2 diabetes mellitus, failure of first-phase insulin secretion with progressive failure of second-phase insulin secretion of the beta cell in conjunction with insulin resistance leads to progression of the disease.[2-5]

Pathogenesis of the Complications of Diabetes

Diabetes mellitus is associated with serious complications, and the incidence and severity of these complications can be reduced through good glycemic control. Several studies have demonstrated that elevated plasma glucose levels correlate with microvascular and macrovascular complications.

Chronic Hyperglycemia.—A retrospective analysis of patient medical records from residents of Rochester, Minn, has provided a wealth of longitudinal data on patients with type 2 diabetes mellitus.[14] The incidence of type 2 diabetes mellitus in this community (overall adjusted rates per 100,000 person-years) was 80.1 for obese patients and 45.6 for nonobese patients.[14] The prevalence of retinopathy in people with diabetes mellitus in the Rochester study was 2.6% at the time of initial diagnosis. The subsequent incidence of retinopathy was 17.4 per 1000 person-years among people free of retinopathy at diagnosis. By 20 years after diagnosis of type 2 diabetes mellitus, the cumulative incidence of retinopathy was 30% and 36%, respectively, for obese and nonobese patients.[15] The cumulative incidence of persistent proteinuria 20 years after diagnosis was 24.6% compared with 8.2% at diagnosis.[16] Risk factors for proteinuria included older age at onset of diabetes mellitus, male sex, elevated initial FPG level, and the presence of retinopathy and macrovascular disease.[16] The risk of chronic renal failure associated with the presence of persistent proteinuria at the time of diagnosis of diabetes mellitus was increased 12-fold, whereas proteinuria developing after diagnosis was associated with a 10-year renal failure risk of 11%.[17]

The Wisconsin Epidemiologic Study was a population-based study designed to evaluate the relationship between glycated hemoglobin and microvascular complications.[18,19] Patients were stratified at the start of the study into younger- or older-onset diabetes mellitus groups and were followed up for as long as 10 years. The study findings showed an increase in the development of retinopathy related directly to baseline glycated hemoglobin levels in both groups of patients. A decrease in glycated hemoglobin levels later in the course of diabetes mellitus may reduce the risk of retinopathy imposed by higher baseline levels in patients with early- and late-onset diabetes mellitus.

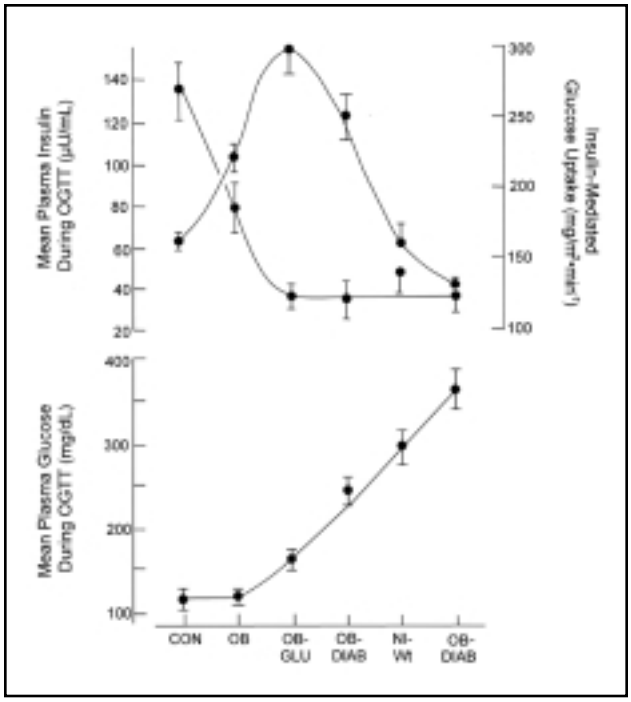

Figure 1. Plasma glucose and insulin responses during 100-g oral glucose tolerance test (OGTT) in control (CON), obese nondiabetic (OB), obese glucose-intolerant (OB-GLU), obese hyperinsulinemic diabetic (OB-DIAB), normal-weight diabetic (Nl-Wt), and obese hypoinsulinemic diabetic (OB-DIAB) subjects. Reprinted with permission from DeFronzo.[2]

The Diabetes Control and Complications Trial (DCCT) was a landmark study that demonstrated the importance of tight glycemic control for patients with type 1 diabetes mellitus.[20] Patients treated with intensive insulin therapy had significant reductions in the incidence of retinopathy, nephropathy, and neuropathy compared with patients receiving conventional therapy.[20]

The Kumamoto study was conducted to evaluate whether the intensive glycemic control seen in patients with type 1 diabetes mellitus in the DCCT would benefit patients with type 2 diabetes mellitus.[21] Results of the Kumamoto study showed that tight glycemic control can effectively delay the onset and progression of microvascular complications in individuals with type 2 diabetes mellitus. The risk reduction with intensive glycemic control seen in this study was similar to the DCCT results.

The United Kingdom Prospective Diabetes Study (UKPDS) is the largest and longest study conducted in patients with type 2 diabetes mellitus.[22,23] The overall objectives of the UKPDS were to determine whether tight glycemic control would reduce the development and progression of complications and whether 1 form of therapy

had specific advantages over another. Patients were assigned to treatment with diet alone, a sulfonylurea, metformin (if obese), or insulin and were then followed up for an average of 10 years. Similar to the DCCT and Kumamoto results, the UKPDS showed that intensive therapy reduces the risk of microvascular complications. Moreover, the study also showed that as long as tight glycemic control was achieved, there was no difference in the effects of the various treatment agents on the risk of microvascular complications. The effect of glycemic control on macrovascular disease was less certain, except for the metformin group, but the adverse result of increased coronary events in the subgroup treated with a sulfonylurea and metformin was disconcerting and inexplicable other than for the study design.

Acute Hyperglycemia.—Experimental studies of acute hyperglycemia have demonstrated effects on renal and nerve function, retinal perfusion, vasodilation, coagulation factors, and atherogenic vascular disease.[24-70] Hyperglycemia may be implicated in glomerular hyperinfiltration, which precedes diabetic renal disease.[24,25] Acute hyperglycemia increases the glomerular filtration rate (GFR) in patients with type 1 diabetes mellitus, and this effect is more pronounced in patients with microalbuminuria/proteinuria.[26,27] Acute hyperglycemia aggravates diabetic nephropathy. The increase in GFR induced by acute hyperglycemia has a rapid onset and is sustained as long as acute hyperglycemia persists.[28] Also, in vitro studies have demonstrated increased production of collagen by mesangial cells exposed to intermittent hyperglycemia.[29,30]

Acutely induced hyperglycemia impairs nerve conduction velocities in diabetic patients and in nondiabetic subjects.[31-34] Acute hyperglycemia can lower pain thresholds in animals and in patients with diabetes mellitus and thereby contributes to neuropathic symptoms.[35,36]

Variations in plasma glucose levels are associated with changes in retinal blood flow.[37,38] Hyperperfusion of the retinal circulation, like renal hyperperfusion, can lead to adverse effects such as the development or the progression of diabetic retinopathy. Hyperglycemia appears to play an important role in retinal hyperperfusion.[37-42] Acute hyperglycemia in normal cats produces an increase in retinal blood flow.[41]

Acute hyperglycemia impairs gastrointestinal motility in diabetic patients and in normal subjects.[43,44] Gastric emptying is delayed.[43-47] This delay may be related to neuropathic changes, but also likely, acute hyperglycemia may produce gastroparesis by a direct effect.[48] This delay in gastric emptying with hyperglycemia is demonstrable in normal subjects.[46] Similarly, acute hyperglycemia has adverse effects on esophageal motility[48] and gallbladder contractility.[49,50]

Acetylcholine-induced vasodilation in vitro is impaired by exposure of the vessel wall samples to acute hyperglycemia.[51] This impairment of vasodilation is glucose dependent.[52] In vivo studies with acute hyperglycemia have shown an increase in blood pressure in both diabetic patients and nondiabetic (normal) subjects.[34,53] Acute hyperglycemia with myocardial infarction[54,55] and stroke[56,57] is associated with an unfavorable prognosis in diabetic and nondiabetic patients[54-58] and in animal studies.[59] Hyperglycemia with stroke aggravates neuronal damage.[58,59] Improved glycemic control with intensive therapy during and after myocardial infarction has a long-term beneficial effect in patients with diabetes mellitus.[60]

Acute hyperglycemia is also accompanied by adverse changes in coagulation factors in diabetic patients and control subjects. The half-life of fibrinogen is shortened,[61] and that of fibrinopeptide A,[62,63] factor VII,[64] and other coagulation factors[65] is increased. Circulating levels of intracellular adhesion molecule 1 (ICAM-1) increase with acute hyperglycemia in diabetic patients with or without vascular disease.[66] ICAM-1 is increased in patients with vascular disease[67] regardless of whether diabetes mellitus is present. ICAM-1 is one of the proadhesion proteins that may accelerate atherogenesis,[68] and it may be considered a marker of activation of the atherogenic process.[69] Adhesion proteins affect the interaction between endothelium and leukocytes[68] and promote atherogenesis.[70]

Thus, acute hyperglycemia in patients with type 1 and type 2 diabetes mellitus is associated with a myriad of metabolic and biochemical abnormalities that are sustained with persistent hyperglycemia and lead to progression of microvascular and macrovascular disease. Two possible mechanisms for the progression to microvascular and macrovascular disease are labile nonenzymatic glycation and free radical formation (oxidative stress).[9,71-77] A discussion of these mechanisms is a separate subject and is referenced here to indicate its interrelationship to the whole topic of basal and prandial glycemia in the development and progression of diabetic complications.

Postprandial Glycemia.—Prandial glycemia is a physiologic response to nutrient intake and represents a fluctuation from basal glucose. Postprandial glycemia remains within a rather tight range of plasma glucose levels between 100 and 140 mg/dL. Postprandial hyperglycemia (glucose level >140 mg/dL) may be associated with a higher frequency of diabetic complications. Postprandial hyperglycemia in patients with type 2 diabetes mellitus is secondary to loss of first-phase insulin secretion and insulin resistance and is associated with hyperinsulinemia, which may relate to increased cardiovascular risk. Hyperinsulinemia is more likely a marker for insulin resistance rather than an etiologic factor in diabetic macrovascular disease.

Any discussion of prandial glycemia must include fasting/premeal glycemia because the two are correlated. High basal FPG levels are associated with exaggerated postprandial glycemic response. With persistent hyperglycemia, beta cell insulin response is lost over time, and low circulating insulin levels occur, necessitating insulin therapy for restoration of first-phase insulin response and improved glycemic control. There may also be up-regulation of peripheral insulin receptors with insulin therapy, and with improved glycemic control, insulin resistance may decrease. Studies of glycemic control have shown lower all-cause mortality in elderly diabetic patients.[78]

Few studies have correlated postprandial glycemia with glycated hemoglobin. Most studies correlate premeal/fasting glycemia with HbA_{1c}. But since elevated basal FPG levels are associated with higher postprandial glucose levels, it is logical to assume that postprandial glycemia is correlated with glycated hemoglobin levels also. In clinical practice, high glycated hemoglobin levels with accurate satisfactory premeal glycemia most likely reflect postprandial hyperglycemia, which needs to be corrected to improve glycated hemoglobin levels.

Several recent studies have indicated that postprandial hyperglycemia may be a better index of glycemic control as measured by glycated hemoglobin than is fasting/premeal basal glucose. Avignon et al[79] observed that postlunch glycemia had better sensitivity, specificity, and predictive value of glycemic control as measured by HbA_{1c} than did fasting or premeal basal glucose level. Hasslacher and Ritz[8] noted a relationship between annual medians of postprandial glycemia and the development of nephropathy in type 1 diabetes mellitus. Ceriello et al[80,81] have shown that the level of postprandial hyperglycemia correlated with overproduction of thrombin, which may increase cardiovascular risk. The total radical trapping antioxidant parameter (TRAP) is reduced with postmeal glycemia in diabetic patients and normal subjects.[9] The decline in TRAP indicates that plasma glucose elevations increase oxidative stress, which may overwhelm the antioxidant defense mechanisms.

There is increasing evidence that both basal FPG levels and postprandial glycemia warrant attention in effecting optimum glucose control to reduce microvascular and macrovascular complications of diabetes mellitus. Previous epidemiological studies have indicated that postmeal glycemia is an important risk factor for macrovascular disease in patients with type 2 diabetes mellitus.[82-89]

The Honolulu Heart Study showed that the risk of fatal and total coronary heart disease (CHD) increased significantly with increasing postmeal glucose levels.[82] The Whitehall Study showed that CHD mortality was double in British men with plasma glucose levels of higher than 96 mg/dL 2 hours after a meal.[83] The prevalence of all CHD (defined as electrocardiographic changes, angina, or myocardial infarction) in the Islington Diabetes Survey increased from 9% in subjects with a 2-hour postmeal glucose level lower than 120 mg/dL to 20% in subjects with glucose levels of 180 mg/dL or higher.[84] The Diabetes Intervention Study also showed that postmeal plasma glucose but not FPG was an independent risk factor for myocardial infarction and CHD mortality.[85] In the DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe),[86] elevated 2-hour postload plasma glucose concentrations were associated with an increased mortality risk, independent of FPG, whereas the association of FPG levels with mortality was dependent on 2-hour postload glucose levels.

Postmeal hyperinsulinemia is also associated with increased risk of coronary disease. The Helsinki Policemen Study, in which insulin levels were examined, showed an association between 1- and 2-hour postmeal plasma insulin levels with fatal and nonfatal CHD events that was not seen with fasting insulin levels.[87] The Paris Prospective Study found that postmeal hyperinsulinemia was a better indicator of CHD mortality than hyperglycemia in male civil servants.[88] The Quebec Cardiovascular Study reported that, over a 5-year period, fasting plasma insulin concentrations emerged as a strong predictor of ischemic heart disease.[89] However, postmeal hyperinsulinemia reflects both beta cell dysfunction and insulin resistance and therefore is most likely a marker of the underlying pathophysiology of type 2 diabetes mellitus rather than an etiologic factor. Nevertheless, postmeal metabolic and biochemical perturbations are associated with increased cardiovascular risk.

These studies demonstrate that elevated glucose levels in the fasting and postmeal states are associated with an increased risk of macrovascular complications that can be reduced with improvement in fasting and postprandial glycemia in glycated hemoglobin levels. It is imperative that the management of type 2 diabetes mellitus address both basal FPG control and control of postprandial changes. Therapy therefore must be targeted to maintain normal basal FPG and normal postprandial glucose levels. To accomplish this end, ideal timing for treatment intervention in patients with type 2 diabetes mellitus is just before a glucose load, when the body is most sensitive to the effects of insulin and is best able to produce it and to control hyperglycemia related to insulin resistance. Exogenous stimulation of early insulin secretion suppresses hepatic glucose production, reduces maximum glucose excursions, prevents delayed hyperinsulinemia, and mini-

mizes fluctuations in plasma glucose levels. Reduction of insulin resistance with insulin sensitizing agents maintains basal glucose levels within the desirable range.

TREATMENT STRATEGIES

A growing number of oral antidiabetic agents and insulin analogues are now available in the United States to target the impaired insulin secretion and reduced insulin sensitivity seen in patients with type 2 diabetes mellitus. These agents have different mechanisms of action and different benefit and risk profiles.

Sulfonylureas

The sulfonylureas have been used to treat type 2 diabetes mellitus for more than 30 years and are recommended when there is inducible pancreatic beta cell function. Beta cells often fail early in the course of type 2 diabetes mellitus. Sulfonylurea therapy fails as a first treatment in 15% to 20% of patients. Patients who had been previously responsive to sulfonylureas have failure rates of 3% to 5% per year.[90]

The sulfonylureas bind to specific membrane receptors on beta cells and inhibit adenosine triphosphate (ATP)–sensitive K^+ channels, resulting in membrane depolarization and Ca^{++} influx, with a release of insulin through exocytosis.[91] The sulfonylureas stimulate early insulin release only, whereas glucose stimulates both early and late insulin secretion through a similar mechanism.[92]

Treatment with equivalent doses of sulfonylureas gives similar results. The second-generation sulfonylureas all decrease FPG levels by approximately 60 mg/dL.[93] Most sulfonylureas are administered 2 to 3 times a day, but newer formulations of second-generation sulfonylureas are long-acting and can be taken once a day. However, sulfonylureas have been associated with hypoglycemia and weight gain.

Repaglinide

Repaglinide, a meglitinide analogue, is a nonsulfonylurea insulin secretagogue. It is a benzoic acid derivative that has a high binding affinity for ATP-sensitive K^+ channels on the beta cells and acts at a different site from sulfonylurea to stimulate insulin release.[94] Repaglinide has a quick onset and short duration of action. Taken with meals, repaglinide has its greatest effect on mealtime glucose levels. Repaglinide is not as effective as sulfonylureas and metformin in reducing FPG and glycated hemoglobin levels, and its primary adverse effect is hypoglycemia.[95]

Nateglinide

Nateglinide is a new oral agent recently approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus. Nateglinide is a D-phenylalanine derivative and produces a rapid, short-lived release of insulin by pancreatic beta cells that is dependent on glucose concentration. Nateglinide increases plasma insulin levels by inhibiting ATP-sensitive K^+ channels on the beta cell[96] through a mechanism of action similar to that of the sulfonylureas and repaglinide but with more rapid potassium channel interaction.[97] As a result of this effect, nateglinide produces a faster release of insulin than other agents. Studies of normal subjects and patients with type 2 diabetes mellitus have shown that nateglinide stimulates early insulin secretion and reduces postmeal glucose excursions when taken before meals.[98] Results of clinical studies suggest that nateglinide restores the physiology of early mealtime insulin release for patients with type 2 diabetes mellitus.

Metformin

Metformin, a biguanide, is equivalent in its efficacy to the sulfonylureas in reducing FPG and glycated hemoglobin levels but has a different mechanism of action. This drug reduces HGP by inhibiting gluconeogenesis and, to a lesser extent, increases uptake and disposal of glucose by muscle.[99] Metformin does not directly affect insulin secretion or increase the risk of hypoglycemia. In addition, metformin has a favorable effect on lipid profiles, decreasing low-density lipoprotein (LDL) cholesterol and triglyceride levels, and it does not cause weight gain; it may even promote weight loss. However, metformin is associated with gastrointestinal disturbances and lactic acidosis and should be used with caution when treating patients with renal impairment.[100-102]

α-Glucosidase Inhibitors

Acarbose and miglitol, the 2 agents in this class, inhibit α-glucosidase, an enzyme present in the brush border of the small intestine. α-Glucosidase breaks disaccharides and polysaccharides into absorbable monosaccharides like glucose, leading to delayed glucose absorption, and peak postmeal plasma glucose levels are then decreased. These agents have a modest effect on glycated hemoglobin, producing a maximum decline between 0.5% and 1.0%. Postmeal glucose is reduced by between 50 and 60 mg/dL. α-Glucosidase inhibitors do not cause hypoglycemia or weight loss. However, they are associated with gastrointestinal adverse effects, predominantly flatulence due to the passage of undigested carbohydrates into the lower bowel.[103,104]

Thiazolidinediones

The overall effect of the thiazolidinediones is improved insulin sensitivity through binding to the peroxi-

some proliferator-activated receptor γ. These receptors enhance control of glucose production, transport, and utilization in skeletal muscle, liver, and adipose tissue. This class has currently 2 available agents: rosiglitazone and pioglitazone.[105,106] Troglitazone was recently withdrawn from use by the FDA because of hepatotoxic effects. The thiazolidinediones are less effective as monotherapy than sulfonylureas and metformin in decreasing FPG and glycated hemoglobin levels. The glitazones as monotherapy do not cause hypoglycemia, but they have been associated with weight gain and increases in LDL cholesterol, which probably represent a larger nonatherogenic LDL particle size.[107-109] Thiazolidinediones are consistently associated with a rise in high-density lipoprotein cholesterol. Rosiglitazone and pioglitazone, the most recently approved agents, are indicated both for monotherapy and combination therapy. Although there is no indication of drug-induced hepatotoxicity with either of these agents, they both carry class warnings, referencing the troglitazone-associated liver toxicity. Recommendations for liver monitoring are included in the labeling of both agents.

Insulin

In type 2 diabetes mellitus, exogenous insulin therapy is indicated for stabilization of patients with severe hyperglycemia and in patients with hyperglycemic crises or in whom oral therapy fails to control glycemic levels. Different formulations of insulin that differ in their time-action profiles (onset, peak, and duration of action) are available for administration by subcutaneous injection. Regular insulin is short-acting, insulin zinc suspension (Lente) and isophane insulin suspension (NPH) are intermediate-acting forms, and insulin zinc suspension (Ultralente) is characterized by slow action.[110] Treatment with these formulations, however, does not closely approximate normal insulin secretion. Lispro insulin, an insulin analogue bearing an inversion of the proline-lysine amino acid sequence at positions 28 and 29 on the B chain,[111] has a pharmacokinetic profile that mimics more closely the physiologic insulin response to nutrients. It has a faster onset and shorter duration of action than regular insulin and is more effective in control of mealtime glycemia.[111] Insulin glargine, designed for the maintenance of basal insulin levels, has a slow absorption rate and a corresponding prolonged duration of action. Over a 24-hour euglycemic clamp study in healthy individuals, insulin glargine demonstrated a 5-hour lag over the onset of action of isophane insulin and a subsequent peakless profile.[112] Used in combination with regular insulin before meals or lispro insulin with meals, insulin glargine can effectively mimic beta cell function to optimize glycemic control.

Combination Therapy

The UKPDS demonstrated the potential problems in attempting to maintain good glycemic control over the long term. The trial showed that by 9 years after disease diagnosis, 75% of the study patients required combination therapy to achieve target FPG and glycated hemoglobin levels. One reason for the difficulty in maintaining good glycemic control with monotherapy is the decline over time in beta cell function and resulting hyperglycemia.[113] Combination therapy offers the advantage of using 2 agents with complementary mechanisms of action, producing synergistic glucose lowering that is greater than can be achieved with each agent used alone. In some cases, lower doses of 1 agent or both can be used, minimizing potential adverse effects and weight gain and reducing abnormal lipid levels. The most widely used and extensively studied combination of oral agents is metformin plus a sulfonylurea. Metformin and glyburide combination therapy was more effective in decreasing FPG and glycated hemoglobin levels after 29 weeks of treatment than either agent used alone.[101] Metformin has also been shown to be effective when used in combination with acarbose, troglitazone, or repaglinide.[103,114,115] The combination of troglitazone with a sulfonylurea is also more effective than either agent used alone in decreasing FPG and glycated hemoglobin levels.[116] However, as noted previously, troglitazone is no longer available for the treatment of diabetes mellitus.

Insulin therapy has also been used in combination with oral antidiabetic agents. A retrospective meta-analysis of a number of controlled clinical trials has demonstrated the efficacy of combined sulfonylurea and insulin treatment in patients with type 2 diabetes mellitus in whom sulfonylurea was no longer effective.[117] The results of the analysis showed that FPG and glycated hemoglobin levels improved with reduced insulin requirements. Metformin[118] or troglitazone[107] in combination with insulin improves glycemic control in patients with type 2 diabetes mellitus.

New Clinical Advances

Recent advances on the development of injectable insulin analogues are aimed at optimizing pharmacokinetic properties for replacement of basal and mealtime insulin. Insulin aspart is a fast-acting analogue bearing an amino acid substitution to aspartic acid at position 28 in the B chain. With a faster onset and shorter duration of action than regular insulin, this analogue improves mealtime glycemic control over the daytime interval in patients with type 1 diabetes, with fewer hypoglycemic events.[119]

With the introduction of more effective insulin analogues, the development of alternative routes of insulin delivery has received considerable attention. Delivery techniques currently being developed or refined include

intranasal, intrapulmonary, and oral formulations,[120] as well as continuous subcutaneous infusions through insulin pumps.[121] Moreover, future improvements in antirejection strategies will increase the potential benefits of pancreas and islet cell transplantation,[122] which are available currently for selected patients.[123]

CONCLUSION

Tight glycemic control should be the goal in treating patients with diabetes mellitus. A renewed interest in the pathophysiology of diabetes mellitus has provided new treatment options based on different mechanisms of action. Recent data suggest that efforts to achieve target glucose levels with an emphasis on early insulin secretion may provide the best measure for modulating the onset of microvascular and macrovascular complications. Treatment with combination therapy may offer the best therapeutic option. The development of the new amino acid derivative, nateglinide, new rapid-acting (lispro insulin, insulin aspart) and long-acting (glargine insulin) insulin analogues, new mechanisms of insulin administration (intranasal, intrapulmonary, oral, and pump therapy), refinement of beta cell and pancreas transplantation, and the development of artificial beta cells will be welcome additions to the treatment options for patients with type 2 diabetes mellitus.

Laura Khan and Jane E. DiGiulio assisted with editing, formatting, and typing the manuscript.

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