Chapter 44
Treating Type 2 Diabetes Mellitus

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Prevalence of DM2

Diabetes currently affects 23.6 million people in the United States, or 7.8% of the population, and 246 million people worldwide.[1,2] Approximately 90–95% of those affected have type 2 diabetes (DM2). Diabetes is the fifth leading cause of death by disease in the United States and was estimated to cost $174 billion in direct and indirect expenditures in 2007.[3] Clearly this is an enormous burden in terms of both human suffering and economic cost.

Rationale for Therapy

Current consensus treatment guidelines from both the American Diabetes association and the European Association for the Study of Diabetes are to lower the A1C to <7% and to get the A1C as close to normal as possible. Glycemic control has been shown to reduce the microvascular and macrovascular complications of the disease. Older adults who are functional, cognitively intact, and have significant life expectancy should be treated to these same goals. Reduction of the A1C to levels closer to normal, as in the ADVANCE trial which targeted an A1C of 6.5% and the ACCORD trial which targeted an A1C of 6%, has not been shown to reduce cardiovascular mortality in those subjects with established cardiovascular disease or those at high risk for cardiovascular disease.[4] In fact, the glucose-lowering arm of the ACCORD trial was stopped because of excess mortality in those participants who were randomized to very tight glucose control – the precise etiology of these deaths is unclear.[5] Despite the fact that intensive glucose control with the goal of achieving an A1C of <6.5% did not reduce risk for cardiovascular events in subjects with established CAD or those at risk for CAD in either the ADVANCE, ACCORD, or VA Diabetes Studies, subjects treated intensively in the ADVANCE trial demonstrated a significant 21% reduction in new or worsening diabetic nephropathy.

One study supporting early intensive therapy for newly diagnosed patients with type 2 diabetes mellitus was the United Kingdom Prospective Diabetes Study or UKPDS. The UKPDS was a randomized multicenter trial that randomized 5102 patients to either conventional dietary management or intensive therapy with either sulfonylurea, insulin, or, if overweight, metformin. The UKPDS showed that early intensive therapy in patients with newly diagnosed DM2 reduced risk of clinically evident microvascular complications by 25%. There was a nonsignificant reduction of 16% in the risk of myocardial infarction.[6] At 10-year follow-up of the UKPDS cohort, there was a significant effect of early intensive therapy on both microvascular and macrovascular disease. In the sulfonylurea–insulin group, microvascular disease risk was reduced by 24% and risks of myocardial infarction and death from any cause were reduced by 15 and 13%, respectively. In the metformin treatment group, there were sustained risk reductions in several key categories: 21% for any diabetes-related end point, 33% for myocardial infarction, and 27% for death from any cause.[7] This study is the first to show that early

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L. Poretsky (ed.), *Principles of Diabetes Mellitus*, DOI 10.1007/978-0-387-09841-8_44,

glycemic control can reduce the incidence of macrovascular as well as microvascular complications in subjects with type 2 diabetes.

According to the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, approximately 55% of people with diabetes do not achieve their target blood sugar levels with their current treatment regimen – despite increasing evidence that glycemic control decreases the incidence of microvascular and macrovascular complications.[8] In addition, two-thirds of adult men and women in the United States with DM2 have a BMI of 27 or greater.[9] Data support that weight loss (even a modest amount) supports patients in their efforts to achieve and sustain glycemic control.[10]

Choice of Initial Therapy

It is important to consider the pathophysiologic defects present in people with type 2 diabetes when considering how to initiate and advance pharmacologic treatment of the disease. Patients with DM2 usually have two major defects contributing to hyperglycemia – insulin resistance and impaired beta cell function. Insulin resistance is often the first "hit": obesity (particularly abdominal and visceral fat) and physical inactivity contribute to this. Nearly all groups at risk for DM2 – Native Americans, African Americans, Mexican Americans – have high rates of insulin resistance and obesity.[11] Insulin resistance causes impaired glucose use and uptake as well as glycogen storage by muscle.[12] Insulin resistance in the liver leads to increased basal hepatic glucose output, as insulin is less efficacious at suppressing gluconeogenesis.[13,14] Initially pancreatic insulin production increases to maintain normoglycemia. With time, the severity of the disease increases with impaired beta cell function which leads to progressive hyperglycemia. Decreased insulin response to both glucose and amino acids leads to postprandial hyperglycemia.[15] The liver also starts to produce more glucose, as the inhibitory effect of insulin declines. Hyperglycemia begets higher blood glucose, as "glucose toxicity" further impairs insulin secretion and action.[16]

Lifestyle Modification

Lifestyle modification is an essential component of any treatment regimen for people with type 2 diabetes. This includes reduction of intake of total calories, saturated and trans fatty acids, cholesterol, and sodium and increased physical activity to improve glycemic control, blood pressure, and dyslipidemia.[17] While this approach alone fails to achieve glycemic targets in the vast majority of patients, change in diet and exercise patterns should be the cornerstone of any treatment plan. Individualized medical nutrition therapy is recommended as needed to achieve weight loss goals and may be helpful in preventing those at risk for the development of type 2 diabetes. The goal of nutrition therapy in people who have diabetes is to use this approach to lower glucose levels as much as possible.[17] An important caveat to the ADA recommendations is that the pleasure of eating should be maintained by limiting food choices only when indicated by scientific evidence.

Physicians should emphasize the necessity for weight loss and strategies for optimizing glycemia through diet modification. These include decreasing dietary fat, increasing whole grain, and dietary fiber intake. There is some suggestion that change in dietary composition alone, independent of energy intake, can improve glucose control. Dietary fat modification, for example, has been shown to improve insulin sensitivity. In one Swedish study, 162 healthy subjects were chosen at random to receive a controlled, isoenergetic diet for 3 months containing either a high proportion of saturated or monounsaturated fatty acids. The study found that decreasing saturated fat and increasing monounsaturated fat improved insulin sensitivity but had no effect on insulin secretion.[18]

In terms of carbohydrate choices, there is a suggestion that a higher intake of dietary fiber decreases risk of developing diabetes and may then be useful in controlling glycemia. From the Nurses Health Study II, one paper examined the association between glycemic index, glycemic load, and dietary fiber and the risk of type 2 diabetes. A subset of 91,249 young women were followed for 8 years for development of DM2. Glycemic index of food intake was significantly associated with an increased risk of diabetes, while cereal fiber intake was associated with a decreased risk of diabetes. Glycemic load was not significantly associated with risk.[19] In the

Insulin Resistance Atherosclerosis Study, 978 middle-aged adults with normal (67%) or impaired (33%) glucose tolerance had improved insulin sensitivity and decreased fasting insulin levels associated with increased whole grain intake.[20] A follow-up study found that no association of glycemic index, glycemic load, or carbohydrate intake associated with insulin sensitivity or with fasting insulin levels after adjusting for total energy intake. Fiber intake, however, was positively associated with improved insulin sensitivity and inversely with adiposity.[21]

In practice, MNT can be remarkably effective in reducing the A1C. There are several randomized trials demonstrating benefit. In the UK Prospective Diabetes Study (UKPDS) 30,444 newly diagnosed patients with type 2 diabetes were randomized to intensive or conventional therapy after 3 months of nutrition counseling from a dietitian. During the initial period of nutritional counseling, the mean HbA1C decreased by 1.9% (from ~9 to ~7%), fasting plasma glucose was reduced by 46 mg/dl, and there were average weight losses of ~5 kg after 3 months.[22]

Another study of 179 individuals with DM2 compared usual nutrition care consisting of only one visit with a more intensive nutrition intervention, which included at least three visits with a dietitian. With the more intensive nutrition intervention, changes in lifestyle significantly improved glucose control. The fasting plasma glucose level decreased by 50–100 mg/dl and the A1C dropped by 1–2%. The average duration of diabetes for all subjects was 4 years and the decrease in A1C was 0.9% (from 8.3 to 7.4%). In the subgroup of subjects with a duration of diabetes <1 year, the decrease in A1C was 1.9% (from 8.8 to 6.9%).[23]

Randomized controlled nutrition therapy outcome studies have documented decreases in A1C of ~1% in newly diagnosed type 1 diabetes, 2% in newly diagnosed type 2 diabetes, and 1% in type 2 diabetes with an average duration of 4 years. MNT should be considered as monotherapy, along with physical activity, in the initial treatment of type 2 diabetes, provided the person has a fasting plasma glucose <200 mg/dl. Individuals with DM2 diabetes who cannot achieve optimal control with MNT and whose disease may be progressing due to beta cell failure should be prescribed blood glucose-lowering medication, along with additional encouragement to achieve goals of MNT and physical activity.[24]

In overweight and obese individuals, weight loss has been shown to decrease insulin resistance. For weight loss, either low-carbohydrate or low-fat diets may be effective in the short term (up to 1 year). It is not established whether the benefits of a high-protein diet are durable, nor what the long-term effects on kidney function are.

Two studies that established the efficacy of lifestyle measures in preventing diabetes include the Finnish Diabetes Prevention Study and the Diabetes Prevention Program or DPP. In the Finnish study, 522 overweight subjects with impaired glucose tolerance were randomly assigned to an intervention or control group. The intervention group received individualized counseling to lose weight and reduce intake of total and saturated fat and to increase intake of fiber and physical activity. Subjects were followed for 3.2 years and received an oral glucose tolerance test annually. Results at the end of 1 year showed a weight loss of 4.2 and 0.8 kg for the intervention and control groups, respectively. The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group. Thus the risk of diabetes was reduced by 58% in the intervention group by lifestyle changes.[25]

The DPP, a multicenter National Institutes of Health study, was a randomized trial involving more than 3200 adults who were >25 years of age and who were at increased risk of developing type 2 diabetes due to impaired glucose tolerance, being overweight and having a family history of type 2 diabetes. The study involved a control group (standard care plus a placebo pill) and two intervention groups: one that received an intensive lifestyle modification (healthy diet and moderate physical activity of 30 min/day for 5 days/week) and one that received standard care plus metformin. Participants in the intensive lifestyle modification group had reduced their risk of developing diabetes by 58% compared with the medication intervention group who reduced their risk by 31%. Even more dramatic was the finding that individuals over 60 years of age in the intensive lifestyle modification group decrease their incidence of developing type 2 diabetes by 71%.[26]

Initiating a Medication

When diet and exercise are not sufficient to control blood glucose, initiation of a medication is indicated. There has been a marked increase in the number of oral and injectable antihyperglycemic agents available over the last

5 years. Currently, there are numerous classes of drugs that can be used to initiate or intensify treatment. These include insulin sensitizers, insulin secretagogues, and agents that delay the absorption of carbohydrate from the bowel. Insulin sensitizers include the biguanide metformin and thiazolidinediones. Insulin secretagogues include sulfonylureas, non-sulfonylurea secretagogues, (GLP-1) agonists, and DPP4 inhibitors. Alpha glucosidase inhibitors delay the absorption of carbohydrate from the GI tract. Finally there is an analogue of amylin, a peptide co-secreted with insulin from the beta cell, pramlintide, which is indicated for use with insulin in patients with both type 1 and type 2 diabetes. Both the American Diabetes Association and the European Association for the Study of Diabetes recommend starting treatment with metformin and continuing to augment therapy with additional agents to maintain recommended glycemic control (i.e., A1C < 7%) in most patients at the time of diagnosis of type 2 diabetes.[27]

Metformin

Metformin is the only biguanide currently in use.[11] Although available internationally for decades, metformin was not approved for clinical use in the United States until 1995. Metformin is the only available medication of this class in the United States, as its predecessor phenformin was discontinued due to its high association with lactic acidosis in 1976. Metformin improves insulin sensitivity and decreases insulin resistance, targeting a primary defect in type 2 diabetes. Metformin suppresses hepatic glucose production and increases glucose utilization, which only occurs in the presence of insulin as metformin enhances insulin action at the postreceptor level in peripheral tissues. The principal site of action of metformin is the liver where it inhibits hepatic glucose production. This drug also enhances glycogen formation and glucose oxidation in muscle.[28] This occurs without increased insulin secretion, thus limiting the risk of hypoglycemia. In fact, insulin levels are stable to decrease with metformin therapy. Metformin also increases glucose utilization by the intestine. This reduction of hepatic glucose production reduces fasting plasma glucose, while the increase in insulin-mediated glucose utilization principally affects postprandial glycemia.

Efficacy

The effect of metformin on glucose control is equal to or superior to other oral agents. Metformin lowers fasting blood glucose by approximately 20% and A1C by about 1.5%. The Metformin Multicenter Study Group compared 143 patients treated with metformin with 146 patients treated with placebo. The metformin group had lower mean fasting plasma glucose (189 ± 5 vs. 244 ± 6 mg/dl) and A1Cs (7.1 ± 0.1 vs. 8.6 ± 0.2%).[29] Metformin also has a favorable effect on metabolism and weight, which is of considerable importance in the typical diabetes type 2 population.

One major benefit of starting with metformin is that it is one of the few medications (other than exenatide and sitagliptin) that does not cause weight gain and is actually associated with mild weight loss. The weight loss is on the order of 2–3 kg, 88% of which is adipose tissue.[30] Metformin does not cause hypoglycemia when used as monotherapy and does not increase plasma insulin levels. In the ADOPT study in patients with recently diagnosed type 2 diabetes, metformin was more effective than glyburide and provided more durable glycemic control with less hypoglycemia and weight gain.[31]

Metformin also has modest benefits on lipid profile. This includes small drop in LDL and triglycerides and a small increase in HDL. The drops in LDL and triglycerides are likely due to reduced hepatic production of VLDL.[32] There may be cardiovascular and mortality benefit beyond these mild improvements in lipid profiles. In the UKPDS, patients' whose body weight was more than 120% of their ideal weight and who used metformin as monotherapy demonstrated a reduction in risk of MI by 39%, and risk of death from any cause was reduced by 36%. At 10-year follow-up, significant risk reductions persisted.

Side effects of metformin are primarily gastrointestinal and may be dose limiting in some patients. Anorexia, metallic taste, nausea, diarrhea, and vomiting may ensue with initiation of therapy. These side effects are usually

mild and transient and may abate with extended release preparations or dose reductions. These side effects may also ameliorate the weight loss effects of metformin if tolerable to the patient. In the clinical trials of metformin, 5% discontinued use of the drug due to gastrointestinal side effects.

Vitamin B_{12} deficiency is more common in patients treated with metformin, with a greater than twofold increased likelihood of vitamin B_{12} deficiency in one study.[33] Metformin may disrupt calcium-dependent vitamin B_{12} intrinsic factor complex in the terminal ileum. This effect is rarely significant enough to cause anemia.

Metformin also causes a small increase in basal and postprandial lactate, likely due to the increased conversion of glucose to lactate by the intestinal mucosa. Lactate then enters the portal circulation, where it can become a substrate for gluconeogenesis or be cleared by the liver.[11] Lactic acidosis is a rare, serious adverse event linked to metformin therapy. The perceived risk is much higher than empiric risk data, likely due to the association with the other biguanide, phenformin. The incidence of lactic acidosis with phenformin was 10–20 times that of metformin. The reported incidence of lactic acidosis with metformin is 3 per 100,000 patient-years. The majority of cases occur in patients with renal insufficiency or illnesses that impair renal function, both of which are contraindications to metformin use. Most cases occur when a condition increasing blood lactate is present, such as hypoxia, hypotension, liver disease, or alcoholism. If metformin is the cause of the lactic acidosis, the medication can be removed by hemodialysis.[34] Metformin should also be stopped in any serious medical condition, particularly when hypotension, impaired tissue perfusion, or increased blood lactate is present or expected.

Contraindications to metformin therapy

Decreased renal function: Plasma creatinine $\geq$1.5 mg/dl for men and $\geq$1.4 mg/dl for women or a creatinine clearance <60 ml/min
Age >80 unless creatinine clearance is $\geq$60 ml/min
Liver disease
Alcohol abuse
Sepsis, myocardial infarction, or acute illness with decreased tissue perfusion
Acute or chronic metabolic acidosis, including diabetic ketoacidosis
During IV radiographic contrast administration

Adapted from the Glucophage XR Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ 08543, USA, October, 2000.

In summary, metformin reduces the A1C by approximately 1.5%, is generally well tolerated, and is not associated with either weight gain or hypoglycemia. Metformin is an appropriate choice for initial therapy of DM2 in most patients. Over time, patients may have progressive hyperglycemia due to progressive beta cell failure. At this point, other medications must be added to achieve target glycemia. Metformin can be combined with sulfonylureas, TZDs, exenatide, sitagliptin, or insulin.

Thiazolidinediones

Thiazolidinediones or TZDs are an attractive therapy for diabetes in that these drugs target the "first hit" in the natural history of diabetes: insulin resistance. TZDs principally work by increasing insulin sensitivity. TZDs bind to and activate one or more peroxisome proliferator-activated receptors (PPARs), which regulate gene expression. Through PPARs, TZDs act on muscle, liver, and adipose tissue to increase glucose utilization and decrease glucose production, but the mechanism through which this occurs is not entirely clear. TZDs lower fasting and postprandial glucose and result in a 1.0–1.6% decrement in the A1C.[35,36]

TZDs initially attracted interest as improvement in insulin sensitivity was thought to modify cardiac risk. TZDs are also associated with numerous vascular benefits, including reducing carotid intima–media thickness, endothelial dysfunction, and restenosis after angioplasty.[37] Pioglitazone, but not rosiglitazone, is also associated with LDL stability and reduction in triglycerides. In a review of six randomized trials, low-density lipoprotein

(LDL) cholesterol levels typically remained constant when monotherapy or combination therapy with pioglitazone was used, while increases in LDL cholesterol levels ranging from 8 to 16% were noted in studies of rosiglitazone.[38] High-density lipoprotein (HDL) cholesterol levels increased by approximately 10% with both drugs. Decreases in triglyceride levels were observed more often with pioglitazone than with rosiglitazone.

There are two TZDs available in the United States, rosiglitazone and pioglitazone, both of which were approved in 1999. Rosiglitazone and pioglitazone are used as monotherapy or with a sulfonylurea, metformin, or insulin. However, there are concerns with combined thiazolidinedione and insulin therapy because of an increased incidence of heart failure.

TZDs are also associated with weight gain, which can be significant. Weight gain is proportional to the dose and duration of therapy. There may be a small increase in appetite and fluid retention is a part of this weight gain. The principal driver of weight gain, however, is thought to be fat cell proliferation with a redistribution of adipose tissue from the viscera to subcutaneous depots.[39] This redistribution from visceral to subcutaneous fat is part of the reason that insulin sensitivity increases while weight increases.[40]

Use of TZDs has declined for several reasons. In addition to associated weight gain and edema, there is recent concern that TZDs increase the incidence of heart failure and cardiac death. One meta-analysis found that while patients given TZDs had increased risk for development of congestive heart failure across a wide background of cardiac risk the risk of cardiovascular death was not increased with either of the two TZDs.[41] Another meta-analysis that received widespread attention reported that the incidence of cardiac events with pioglitazone therapy was significantly less than with rosiglitazone therapy.[42] While the conclusions of this study remain controversial, concerns of cardiotoxic effects of TZDs persist pending the results of additional trials currently underway.

TZDs can be used in combination with metformin, insulin, sulfonylureas, exenatide, and sitagliptin but is not often selected for add-on therapy due to the associated fluid retention, weight gain, and ambiguity regarding cardiovascular effects described above. Rosiglitazone carries an FDA black box warning against potential increased risk of heart attack, and both drugs have black box warnings regarding increased risk of congestive heart failure. Nevertheless, these drugs are quite efficacious in controlling glycemia.

Sulfonylureas

Sulfonylureas (SUs) are a class of commonly prescribed antidiabetic drugs used to increase insulin secretion. All secretagogues have the following mechanism of action as they all bind to the SU receptor. SUs stimulate insulin secretion by causing the closure of the adenosine triphosphate (ATP)-dependent potassium channel (K_{ATP}) in the plasma membrane of the beta cell. When a sulfonylurea binds to the sulfonylurea receptor, or when plasma glucose levels are elevated, the K_{ATP} channel closes. When the K_{ATP} channel closes, potassium accumulates at the plasma membrane causing the depolarization of the membrane. When the membrane depolarizes, voltage-dependent calcium channels open and Ca^{2+} enters the intracellular compartment. The increase in Ca^{2+} stimulates migration and exocytosis of insulin granules. SUs also increase responsiveness of beta cells to both glucose and non-glucose secretagogues such as amino acids, resulting in more insulin secretion.

Clinical use of SUs in the United States dates back to 1954, when the first generation of these drugs was introduced. Second-generation SUs are more potent, allowing lower doses, and safer due to shorter duration of action than the first-generation agents. There are three so-called second-generation sulfonylureas on the market in the United States: glyburide, glipizide, and glimepiride. SUs are fairly efficacious, resulting in an average 1–2% decrement in A1C when used as monotherapy.[43,44] The duration of action of second-generation SUs ranges from 12 to 24 h and they are generally given in once-a-day or divided doses. The longer acting agents (for example, glyburide) better suppress morning hepatic glucose production and thus result in lower fasting blood glucose. However, this longer duration of action also results in more hypoglycemic episodes.

The principal side effects from SUs are the weight gain and risk of hypoglycemia that often accompany their use. Weight gain is typically on the order of 2–5 kg, which is counterproductive in this group of patients.[16,6] Sulfonylurea therapy eventually fails to provide adequate glycemic control in the majority of patients with type 2 diabetes; the durability of efficacy is a known issue but may be related to the natural history of diabetes rather than the mechanism of action of the drugs.

There is also a controversy regarding a potential association between SUs and cardiovascular morbidity.[16] The first suggestion regarding this link came from the University Group Diabetes project, which found an increased cardiovascular mortality in the group randomized to treatment with SUs versus insulin.[45] Because of questions related to methodology, several studies attempted to replicate these results. A retrospective cohort study of 5795 newly diagnosed type 2 diabetic patients from Canada, for example, compared levels of exposure to monotherapy with first- and second-generation sulfonylureas and metformin to determine whether increased mortality was associated with increased drug exposure. Risk of death increased twofold with higher daily doses of the first-generation sulfonylureas and 40% with glyburide, but not metformin. Similar associations were observed for death caused by an acute ischemic event.[46] The mechanism of this association with cardiovascular events is unclear. One thought is that because there are sulfonylurea receptors in the heart, use of SUs at the time of a myocardial infarction prevents adequate cardiac vasodilatation and resulting in more myocardial damage. Glimepiride, a second-generation agent, preferentially binds to the pancreatic beta cell SU receptors versus other agents and may not have the same cardiac risks, although this has not been proven. SUs carry a black box warning as mandated by the FDA that these agents may increase risk of cardiovascular disease. Despite this there is no clear evidence that SU use is associated with any increase in cardiovascular mortality – this was demonstrated in the UKPDS which showed no increase in cardiovascular mortality in subjects taking SUs when compared to those taking metformin or insulin.

SUs are typically metabolized by the liver and cleared by the kidney, limiting their use in patients with liver or kidney disease. SUs can be used as monotherapy or combined with all of the other oral therapies, exenatide and insulin.

The Meglitinide Analogues: Non-sulfonylurea Secretagogues

The rationale for development of non-SU secretagogues was to target a principal defect in DM2: inadequate prandial insulin response or so-called early-phase insulin response. In DM2, mealtime insulin response is delayed and blunted, whereas normal prandial insulin increases rapidly and peaks within 1 h.[47] The loss or attenuation of early-phase insulin secretion in type 2 diabetes results in inadequate insulin suppression of hepatic glucose production.[48] The aim of the non-SU secretagogues is to increase mealtime insulin secretion and reduce risk of hypoglycemia in the postabsorptive phase after the meal.

There are two non-SU insulin secretagogues available in the United States, repaglinide and nateglinide. These medications spur rapid and short-lived secretion of insulin from the pancreas. The mechanism of action of these medications is similar to that of SUs, as they bind to the SU receptor, but the duration of action is much shorter. This results in increased insulin secretion right after the meal, as well as less risk of hypoglycemia.[49] The non-SU secretagogues are rapidly absorbed, metabolized primarily by the liver, and more than 90% excreted in bile.

In terms of efficacy, the secretagogues are similar to metformin, but only repaglinide is comparable to the SUs. Repaglinide reduces A1C by about 0.7[50] to 1.5%.[51] In a head-to-head trial, repaglinide was similar to SUs with regard to glucose-lowering effects.[52] The major advantage of non-SU secretagogues over SUs is their shorter duration of action. Because the medication is cleared within 4 h and insulin levels return to baseline within 2 h, the risk of hypoglycemia when skipping a meal (and thus a dose) is low.[53] One study of 6000 patients with DM2 showed that before switching to repaglinide, 38% of patients ate when not hungry due to fear of hypoglycemia. This figure was reduced to 10% when repaglinide replaced usual therapy.[54] An added benefit of these short-acting agents is that patients do not need to eat when not hungry due to fear of hypoglycemia and do not gain as much weight as a result.

Another advantage of repaglinide over sulfonylureas is predominately hepatic clearance, with less than 10% renally excreted. This allows mealtime dosing in patients with renal disease who have a higher risk of hypoglycemia with sulfonylureas. The plasma half-life of repaglinide is extended in patients with severe renal impairment (from 1.5 to 3.6 h) but can be used without any special precautions in patients with mild-to-moderate renal impairment. Nateglinide is hepatically metabolized, with renal excretion of active metabolites. With decreased renal function, active metabolites can accumulate and cause hypoglycemia.

Both repaglinide and nateglinide are dosed before meals and can be used in combination with metformin or a TZD.

α-Glucosidase Inhibitors

Two α-glucosidase (AG) inhibitors, acarbose and miglitol, are available in the United States. AG inhibitors are a distinct class of antihyperglycemic agents that does not target a pathologic defect in DM2 but instead targets the enzyme α-glucosidase. α-Glucosidase is an enzyme that acts in the brush border of the proximal intestine to metabolize disaccharides and complex carbohydrates. Inhibition of the enzyme results in delayed carbohydrate absorption and blunted postprandial glucose excursions. This is coupled with a small reduction in postprandial insulin secretion, likely owing to the smaller rise in blood glucose. The overall efficacy of AG inhibitors is not as pronounced as some of the other oral agents, with average reduction in A1C by approximately 0.5–1.0%.[55] But there is no weight gain or hypoglycemia associated with the medication, a considerable advantage.[56] Many patients have trouble tolerating the primary side effects of flatulence, diarrhea, and abdominal discomfort. In one study of 893 patients treated with *acarbose*, only 16–20% were still taking the drug after 1 year and half of them stopped the drug during year 2.[57] Slow dosage increases minimize gastrointestinal side effects. The usual initial dose is 50 mg before meals. With higher doses the occurrence of side effects increases without improved effect on glycemia.[58]

There is conflicting data as to whether AG inhibitors favorably alter serum lipids. One study found that LDL cholesterol decreased and HDL cholesterol increased in response to therapy,[59] but a larger meta-analysis found no significant effect. That meta-analysis found no association with morbidity or mortality with use.[60] There may be a small decrement in body weight associated with use.

The Incretin System

With the exception of metformin, one frustration for both patient and physician with the available therapies is that they cause weight gain – in addition to other adverse effects including edema and risk of hypoglycemia. This led to considerable interest in a novel approach to treating diabetes type 2 by employing so-called incretin hormones. Eating triggers the secretion of numerous gut hormones that regulate motility and secretion of pancreatic enzymes, bile and stomach acid. These gut hormones also stimulate insulin secretion. The observation that enteral nutrition stimulates more insulin release than parenteral nutrition led to the development of the "incretin concept."[61] The incretin effect is the increase of glucose-stimulated insulin release in the presence of nutrients in the gut. Subsequently, several gut-derived hormones involved in glucose homeostasis were identified. The principal of these incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). GLP-1 is the only incretin hormone used clinically.

GLP-1 is synthesized in the enteroendocrine L cells in the distal ileum and colon, but GLP-1 secretion is likely triggered by endocrine and neural signals when food is sensed more proximally in the small intestine or stomach.[62] GLP-1 levels are low in the fasting state and increase soon after eating. Incretin hormone levels decline rapidly, though as they are rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP4) resulting in a half-life on the order of minutes. GLP-1 receptors are present on myriad tissues; most relevant are the beta islet cells of the pancreas, central nervous system (including the hypothalamus), and adipose tissue. But GLP-1 receptors are also present in the peripheral nervous system, heart, lung, liver, kidney, and gastrointestinal tract. In the pancreas, GLP-1 causes increased insulin secretion. Sustained levels increase insulin synthesis and beta cell proliferation. The effect of incretins is glucose dependent; blood glucose must be >55 mg/dl to produce an effect.[63] There is also some promising evidence that GLP-1 enhances beta cell survival, which may delay the progression of DM2.[64] GLP-1 also helps to control blood glucose by inhibiting glucagon secretion, slowing gastric emptying, and actually decreasing food ingestion. This last effect is important in addressing the central cause of most type 2 diabetes mellitus: obesity.

The evidence for the anorexigenic effects of GLP-1 comes from both human and animal testing. Intracerebroventricular administration of GLP-1 reduces calorie intake in animal models, while the GLP-1 receptor antagonist exendin 9–39 increases food intake.[65] Obese people have less GLP-1 secretion in response to eating than lean people, and weight loss improves GLP-1 levels.[66] Patients with DM2 also have reduced GLP-1 secretion with meals. Reduced GLP-1 secretion could, therefore, contribute to obesity, and replacement may restore satiety. This effect is thought to be primarily due to delayed gastric emptying, but the CNS studies in animals also suggest that GLP-1 may suppress appetite centrally. Central administration is not necessary of course: obese subjects receiving subcutaneous GLP-1 for 5 days, just before each meal, reduced their calorie intake by 15% and lost 0.5 kg in weight.[67]

Actions of incretin hormones
Increased insulin secretion, especially at meals (incretin effect)
Suppression of glucagon secretion, except during hypoglycemia
Increased synthesis of proinsulin
Increase in pancreatic islet cell mass
Inhibition of beta cell apoptosis
Slowed gastric emptying
Increased satiety
Weight loss

Adapted from Drucker and Nauck.[62]

There are currently only two FDA-approved medications that manipulate the incretin system to modulate blood glucose. These are exenatide, a GLP-1 analogue, and sitagliptin, a DPP4 inhibitor. Other GLP-1 analogues, including a one-weekly formulation, as well as alternative DPP4 inhibitors are currently in development.

GLP-1 Analogues

The FDA approved the first incretin mimetic, exenatide, in April 2005. Exenatide is a synthetic form of exendin-4, which was discovered during an investigation for active peptides in lizard venom.[68] Exendin-4 has approximately 50% homology to mammalian GLP-1 and thus binds to the GLP-1 receptor and has the distinct advantage of being DDP4 degradation resistant. GLP-1 analogues require injection, however, and each injection lasts approximately 4–6 h in plasma circulation. The starting dose of exenatide is 5 μg twice daily – generally before breakfast and dinner – for the first 4 weeks, followed by a dose increase to 10 μg twice daily. Exenatide reduces A1C by about 0.8–1.0% over 30 weeks and is associated with modest weight loss of approximately 1.5–3 kg. The open-label extension demonstrated continued weight loss of 4–5 kg after 80 weeks.[69] There has been no difference demonstrated between exenatide and insulins glargine or biphasic aspart in open-label noninferiority studies, but these agents are associated with weight gain and risk of hypoglycemia.[70,71]

Liraglutide, a partially DPP4-resistant GLP-1 analogue, is in phase 3 clinical trials and is being reviewed by the FDA at the time of writing. Liraglutide has a longer half-life than exenatide and can be given as a once-daily injection but is otherwise quite similar in mechanism of action. Liraglutide reduces A1C by up to 1.75% with concomitant weight loss and transient nausea, vomiting, and diarrhea.[72]

There is also a long-acting exenatide in phase 3 clinical trials which has not yet been approved for clinical use. Exenatide long-acting release (LAR) formula is injected weekly instead of twice daily – clearly advantageous from the patient perspective. Preliminary data suggest that exenatide LAR is more potent, with greater decreases in mean A1C over 30 weeks with no increased risk of hypoglycemia and similar reductions in body weight.[73] This effect is likely due to increased suppression of glucagon and resultant decrease in fasting glucose with essentially continuous GLP-1 analogue. The twice-daily formula is more effective for control of postprandial hyperglycemia.

There is a risk of hypoglycemia with GLP-1 analogues but mostly when used in conjunction with sulfonylureas.[74,75] Off-label usage with insulins would clearly increase this risk. Side effects are generally

gastrointestinal, principally nausea plus/minus vomiting. Nausea peaked in clinical trials in the first 8 weeks of therapy and then waned. Incidence of severe nausea was 5–6%, but overall incidence of gastrointestinal side effects of any kind was common – approximately 15–40% depending on the compound and trial – but rarely severe enough to spur trial withdrawal.

In addition, there may be an association between exenatide and pancreatitis. The FDA reviewed 30 postmarketing reports of acute pancreatitis and an additional six of hemorrhagic pancreatitis in patients taking exenatide (Byetta®). An association between Byetta® and acute pancreatitis was suspected in some of these cases. There are no known patient characteristics that determine when pancreatitis associated with Byetta will be complicated by the hemorrhagic or necrotizing forms of this condition. If pancreatitis is confirmed, exenatide should be stopped and not restarted. The FDA recommends that other antidiabetic therapies be considered in patients with a history of pancreatitis. The FDA asked the maker of Byetta, Amylin Pharmaceuticals, Inc., to include information about acute pancreatitis in the "Precautions" section of the product label.

Exenatide is approved for use in the United States with sulfonylurea, metformin, and/or a TZD; insulin is a notable exception to this list. Several other GLP-1 agonists and formulations are in development.

DPP-4 Inhibitors

Because the GLP-1 analogues are injectable, there is considerable interest on oral incretin therapy. DPP-4 degrades endogenous GLP-1, resulting in a short half-life. The DPP-4 inhibitors block degradation, resulting in prolonged action of GLP1. While DPP-4 inhibitors are not associated with weight loss, these agents are "weight neutral" and are associated with few side effects. The risk of hypoglycemia is increased only due to combination therapy, such as with insulin and sulfonylureas.

Not surprisingly, the DPP-4 inhibitors decrease glycemia by a similar mechanism to GLP-1. They augment insulin secretion and inhibit glucagon release, leading to enhanced suppression of endogenous glucose production.[76] The only DPP-4 inhibitor available in the United States is sitagliptin, which was approved by the Food and Drug Administration in October 2006 for use as monotherapy or in combination with metformin, TZDs, or SUs. Another DPP-4 inhibitor, vildagliptin, was approved in Europe in February 2008, and several other compounds are under development. In clinical trials performed to date, DPP4 inhibitors lower HbA1C levels by 0.6–0.9% points are weight neutral and relatively well tolerated without significant gastrointestinal upset.[77,78] In combination with metformin, the decrement in A1C is approximately 2%. Markers of insulin secretion and beta cell function were also significantly improved with sitagliptin.

GLP-1 agonists and DPP-4 inhibitors both effectively increase GLP-1. Exenatide can be added to one or more oral therapies when those therapies are inadequate, often as an alternative to insulin. Sitagliptin can be used as monotherapy or add-on therapy to other oral agents. DPP-4 inhibitors are not associated with weight loss but do not cause weight gain. There is no associated nausea, vomiting, or delayed gastric emptying.

DPP-4 inhibitors have not been associated with characteristic infections, but the incidence of upper respiratory and urinary tract infections is increased in clinical trials. Because DPP-4 is present in cell membranes, including those of lymphocytes, there are some theoretical concerns regarding impaired immune function. There was also increased risk of headache seen in meta-analysis of DPP-4 inhibitor trials.[63]

Amylin Agonists (Pramlintide)

Pramlintide is a synthetic analogue of the beta cell hormone amylin, which is co-secreted with insulin from the pancreatic beta cell and which is deficient in diabetes. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions.[79] In terms of glycemic control, pramlintide is moderately effective with A1C decrements of 0.5–0.7% in clinical trials. Adverse effects include nausea and hypoglycemia.[80] Approximately 30% of treated participants in the clinical trials have developed nausea, but this side effect tends to abate with

time on therapy. Weight loss associated with this medication is ~1–1.5 kg over 6 months, some of which may be due to gastrointestinal side effects and increased satiety due to slowed gastric transit. Pramlintide is approved for use only with insulin, but trials as a weight loss medication, both alone and in combination with leptin, are underway.

Insulin

Because of the decline in beta cell function over time,[81] many patients with type 2 diabetes eventually require insulin therapy. Oral hypoglycemic agents lose efficacy over time in part due to loss of insulin secretory capacity of the beta cell. In the UKPDS, for example, 50% of the participants originally controlled with monotherapy needed the addition of another agent after 3 years and 75% needed multiple therapies at 9 years.[82] Insulin therapy is indicated when adequate glycemic control is not achieved using diet, exercise, and one or more oral agents. Although insulin is both the most physiologic and the effective medication to lower blood glucose, most patients are reluctant to proceed to insulin and many physicians are loathe to start insulin therapy for a variety of reason. Many patients view the need for insulin as a personal failure or a harbinger of doom. Other reasons why patients and physicians are often reluctant to start insulin include concerns about weight gain and hypoglycemia. The progressive nature of type 2 diabetes should be reviewed with patients early in the course of disease management so that they understand why insulin treatment may be necessary. In addition the issues of weight gain and risk of hypoglycemia need to be addressed with patients, in particular the risk of hypoglycemia which is very low in patients with type 2 diabetes taking insulin.

Under normal, nondiabetic circumstances, insulin is secreted in a pulsatile manner under basal, unstimulated conditions and in response to meals.[83] In 24 h, approximately 50% of insulin production is basal and 50% is prandial. Basal insulin is secreted overnight and between meals to suppress hepatic glucose production. These proportions should guide exogenous insulin therapy. There are many types of insulin available, and the differing pharmacokinetics of these agents can be used to mimic pulsatile physiologic insulin release via multiple daily injections. The details of the onset and duration of actions of these insulins are detailed elsewhere in this book (Chapter 43). Generally, insulins can be grouped by pharmacokinetics: rapid-, short-, intermediate-, and long-acting. Longer acting insulins are used as basal insulin one or two times daily, while short- and rapid-acting insulins are used for mealtime coverage. Premixed insulins combine basal and prandial insulin, generally comprised of short- and intermediate-acting insulins in a wide range of ratios (90:10 to 50:50). The regimen that best mimics normal pancreatic function is the so-called basal-bolus regimen. Once or twice per day basal (long- or intermediate-acting) insulin is employed to mimic the fasting and postabsorptive state, and bolus (rapid- or short-acting) insulin is used at mealtime. The rapid-acting insulins produce less postprandial hypoglycemia than short-acting insulins,[84] largely related to duration of action. Long-acting insulin analogues are associated with less hypoglycemia due to a less pronounced peak in insulin action compared to NPH.[85]

Premixed insulins, which combine a rapid-acting with intermediate-acting insulin, generally provide good but not excellent control. These insulins are generally given twice daily but are occasionally given three times daily before all meals. Certainly premixed insulin have a significant advantage over basal insulin alone, given the rapid-acting prandial control and result in a significantly better reduction in HbA1C.[86] Premixing avoids errors from mixing by the patient in a syringe and reduces the numbers of injections, which is advantageous in the elderly, those with visual or fine-motor impairment.[87] But premixed insulins are in a fixed ratio, which limits flexibility to titrate the mealtime and basal components because dose increases may predispose to early or late hypoglycemia.

For most patients with type 2 diabetes who are not achieving therapeutic goals on oral medications, initial therapy with insulin usually consists of the addition of basal insulin to the regimen of oral hypoglycemics. Addition of basal insulin can lower the A1C by up to 1.6%. One study showed that the impact of postprandial hyperglycemia on HbA1C increases with improved control. Postprandial glycemic control was found to account for 70% of overall glycemic control when the HbA1C is less than 7.3% but 50% when the HbA1C is between 7.3 and 8.4%.[88] In various "Treat-to-Target" trial, once-daily basal insulin targeting fasting plasma glucose

levels allowed the majority of patients to achieve a HbA1C of less than 7%.[89] In these studies, once-daily NPH and detemir or NPH and glargine were equally efficacious, but NPH was associated with significantly more episodes of hypoglycemia than either of these basal analogues, in particular nocturnal hypoglycemia. Insulin can be combined with metformin, sulfonylureas, meglitinides, and thiazolidinediones. Of note, despite a theoretic synergy of basal insulin with prandial incretin therapy, these combinations are not yet approved. We do not recommend discontinuing oral antidiabetes medications when insulin is initiated, since there is synergy and an "insulin-sparing" effect when insulin sensitizers,[90] including metformin, are continued. Limiting insulin doses may be helpful in minimizing insulin-related weight gain.

The ADA and EASD recommend starting with a bedtime intermediate-acting insulin or morning or evening long-acting insulin at 10 units or 0.2 U/kg. This dose should be titrated upward by 2–3 units every 3 days until the fasting morning glucose is at goal (70–130 mg/dl).[27] While more physicians are using long duration insulin analogues that have a more "flat" profile of action, NPH may be a more appropriate choice in patients who have significant increases in blood glucose over the course of the early morning.

If the HbA1C is still above goal 2–3 months after initiating basal insulin, preprandial blood glucose patterns should be examined. If the prelunch is elevated, then rapid-acting insulin should be added at breakfast. If the predinner value is elevated, then NPH could be added at breakfast or rapid-acting insulin at lunch. If prebedtime glucose is elevated, rapid-acting insulin is needed at dinner. The addition of presupper prandial insulin to a bedtime basal insulin can be achieved sometimes by substituting a premixed insulin analogue at supper and stopping the bedtime basal insulin analogue or NPH. If this fails to get the A1C to goal, then it is likely that prandial insulin at breakfast and lunch will be needed – this can be achieved by using prandial insulin alone at the meal or using premixed insulin once, twice, or sometimes three times daily. There is no true "maximal dose" of insulin, although variability of insulin absorption increases with higher doses.[91] In type 2 diabetes, insulin requirements are typically greater than in type 1 due to insulin resistance. Doses often exceed 1 U/kg to achieve normoglycemia in type 2 diabetes.

Side effects of insulin include weight gain and hypoglycemia. The weight gain associated with insulin can be marked and create a circle of increasing insulin requirements due to increased body size, leading to further weight gain. In the DCCT, mean weight gain after the first year was 3.6 ± 4.8 kg and 3.0 ± 4.1 kg for men and women, respectively, with intensive therapy.[92] Weight gain varied at 9-year follow-up. Less than 5% of men and 15% of women in the conventional treatment group had major weight gain (20% of baseline or approximately 14 kg), compared with about 35% of women and <30% of men in the intensive treatment group. In the UKPDS, mean weight gain after 10 years of insulin therapy was about 7 kg for subjects with type 2 diabetes on intensive treatment with sulfonylureas or insulin, with the most rapid weight gain occurring when insulin was first initiated.[93] Intensive therapy with insulin in the DCCT also caused a relatively high rate of hypoglycemia of 61 per 100 patient-years.[94] However studies of insulin use in type 2 diabetes have shown significantly less hypoglycemia than that observed in patients with type 1 diabetes. Insulin analogues with longer durations of actions may decrease the risk of hypoglycemia compared with NPH. Rapid-acting insulin analogues, called rapid-acting insulins, may reduce the risk of hypoglycemia compared with regular insulin,[27,95] due to pharmacokinetics that are more closely matched to postprandial glycemic patterns.

With intensive basal-bolus regimens, excellent glycemic control can be achieved, but patients need to test glucose levels more frequently: hypoglycemia. Premixed insulins may be more convenient for some patients but provide patients with less "flexible" lifestyle options in that ideally they should follow more consistent carbohydrate intake at meals and have meals at roughly similar times each day. With the variety of preparations of insulin with different pharmacokinetics, patient regimens can be individualized to meet the metabolic and lifestyle needs of the patients. Age, patient motivation, general health, and goals of treatment should all be considered in choosing an appropriate regimen.

Conclusions

There are numerous medications available to achieve glycemic targets. While many organizations recommend use of metformin at the time of diagnosis of type 2 diabetes, lifestyle modification remains an essential

component of any treatment regimen. If this alone is recommended as initial treatment, then medications should be started within 3 months if A1C targets are not achieved. In the absence of contraindications, metformin should be the initial choice of therapy. Sulfonylureas are usually the next logical choice due to their long safety profile and low cost. But in an elderly patient or patient with renal impairment, where the risk of hypoglycemia may be increased, another medication like a DPP4 inhibitor or non-SU secretagogue may make more sense. In an obese patient, a trial with exenatide should be considered despite frequent GI side effects and lack of long-term data. The following is a summary of available therapies as recommended by the ADA and EASD:

Summary of Glucose-Lowering Interventions

Intervention	Expected decrease in HbA1C (%) with monotherapy	Advantages	Disadvantages
Tier 1: Well-validated core			
Step 1: Initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: Additional therapy			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: Less well validated			
Thiazolidinedione	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive

[a]Repaglinide more effective in lowering HbA1C than nateglinide.
Reproduced from Nathan et al.[96]

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