Treating Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes is a growing problem within the United States and worldwide. Lifestyle modification remains the cornerstone of management, though additional treatment with antihyperglycemic agents is often required. Appropriate management of hyperglycemia is necessary to prevent acute complications and to reduce the risk of long-term complications, including microvascular and macrovascular disease. Treatment goals and management strategies should be individualized to each patient. Fortunately, the majority of patients can be well controlled with currently available agents if managed appropriately. Herein, we review the basic pathophysiology of type 2 diabetes and use this knowledge to review different therapeutic options for managing hyperglycemia associated with type 2 diabetes.

Keywords

Type 2 diabetes • Metformin • SGLT-2 inhibitors • GLP-1 receptor agonists • Sulfonylureas • Thiazolidinediones • Insulin

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Prevalence of DM2

Diabetes currently affects 29.1 million people in the United States, or 9.3% of the population, and more than 350 million people worldwide [1]. The prevalence among Americans aged 65 years and

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older is even greater at 25.9% [2]. Approximately 90–95% of those affected have type 2 diabetes (DM2). Diabetes is the seventh leading cause of death by disease in the United States and was estimated to cost $245 billion in direct and indirect expenditures in 2012, an increase from $174 billion dollars 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 HbA1C to <7% and to get the HbA1C as close to normal as possible provided this can be achieved safely [4, 5]. Glycemic control has been shown to reduce the microvascular and macrovascular complications of the disease [6]. Older adults who are functional and cognitively intact and have significant life expectancy should be treated to these same goals. Initial studies evaluating effects of reducing 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%, did not show any reduction in cardiovascular mortality in those subjects with established cardiovascular disease or those at high risk for cardiovascular disease [7]. In fact, the glucose-lowering arm of the ACCORD trial was stopped early because of excess mortality in those participants who were randomized to very tight glucose control – the precise etiology of these deaths is unclear [8]. 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 (coronary artery disease) 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. Further, follow-up of subjects in the VADT study revealed that those treated intensively demonstrated a 17% reduction in cardiovascular events but no change in cardiovascular mortality [9].

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 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 [43]. At 10-year follow-up of the UKPDS cohort, there was a significant effect of early intensive therapy on both microvascular disease 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 [10]. This study is the first to show that early 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, over 40% of people with diabetes do not achieve their target blood glucose levels with their current treatment regimen – despite increasing evidence that glycemic control decreases the incidence of microvascular and macrovascular complications [11]. In addition, two-thirds of adult men and women in the United States with DM2 have a BMI of 25 or greater [12]. Data indicates that weight loss (even a modest amount) supports patients in their efforts to achieve and sustain glycemic control [13].

Choice of Initial Therapy

It is important to understand 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 leading to hyperglycemia – insulin resistance and impaired beta cell function. Insulin resistance is often the first "hit": obesity (particularly abdominal and visceral fat), genetic predisposition, and physical inactivity contribute to this. Nearly all groups at risk for DM2 – Native Americans, African Americans, and Mexican Americans – have high rates of insulin resistance and obesity [14]. Insulin resistance causes impaired glucose use and uptake as well as impaired glycogen storage by muscle [15]. Insulin resistance in the liver leads to increased basal hepatic glucose output, as insulin is less efficacious at suppressing gluconeogenesis [16, 17]. Initially pancreatic insulin production increases to maintain normoglycemia; however 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 [18]. Hyperglycemia begets higher blood glucose, as "glucose toxicity" further impairs insulin secretion and action [19]. Accelerated lipolysis in fat cells, incretin deficiency/resistance in gastrointestinal tract, increased glucagon secretion, enhanced renal glucose absorption, and central insulin resistance compound the insulin resistance and beta cell dysfunction, leading to the worsening of hyperglycemia [20]. Through understanding the pathophysiology of type 2 diabetes, it is easier to guide treatment choices and leads to better understanding of the need for multiple drugs to target different pathological defects.

Lifestyle Modification

Lifestyle modification is an essential component of any treatment regimen for people with type 2 diabetes and those at risk for type 2 diabetes. This includes reduction of intake of total calories, saturated fats, and sodium, preferred use of low glycemic index carbohydrates, increasing whole grain and dietary fiber intake, and increased physical activity to improve glycemic control, blood pressure, and dyslipidemia. 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 this disease. The goal of nutrition therapy in people who have diabetes is to use this approach to lower glucose levels as much as possible. 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 [21].

Lifestyle measures may be effective in preventing diabetes, as demonstrated in 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 kg 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 [22]. The 7-year follow-up suggested maintenance of lifestyle changes among the intervention group with ongoing 43% relative risk reduction in development of diabetes [23].

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%[24]. Ten-year follow-up showed ongoing benefit with 34% decreased incidence of diabetes in the lifestyle group and 18% decreased in the metformin group relative to placebo [25].

In overweight and obese individuals with type 2 diabetes who may already be on medications, weight loss and medical nutrition therapy (MNT) have been shown to decrease insulin resistance and improve cardiovascular risk factors above and beyond medications alone. The randomized Look AHEAD trial evaluating 5,145 subjects with type 2 diabetes with BMI >25 kg/m^2 compared intensive lifestyle interventions (including group and individual meetings focused on decreased caloric intake and increased physical activity) to standard diabetes support and education. Those in the intensive intervention group had an improvement in A1c of 0.7% compared to 0.1% in control group, along with improvements in systolic and diastolic pressures, triglycerides, and HDL [13].

These studies suggest that MNT is the foundation for optimal diabetes control and weight management. Physicians should emphasize the necessity for weight loss and strategies for optimizing glycemia through diet modification. 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 [26]. Multiple subsequent studies evaluating the effect of a Mediterranean diet, rich in monounsaturated fats, have confirmed that this diet results in improvement in glycemic control and serum lipids [27, 28]. Additional studies suggest that higher intake of dietary fiber decreases risk of developing diabetes and improves glycemic control. The Nurses' Health Study II examined the association between glycemic index, glycemic load, and dietary fiber and the risk of type 2 diabetes; results suggested that a higher 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 [29]. 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 [30]. Fiber intake was also positively associated with improved insulin sensitivity and inversely with adiposity [31].

In clinical practice, medical nutrition therapy (MNT) can be remarkably effective in reducing the A1C. The UK Prospective Diabetes Study (UKPDS) evaluated 30,444 newly diagnosed patients with type 2 diabetes who 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 [32]. Smaller studies have compared usual nutrition care consisting of one nutrition visit with a more intensive nutrition intervention, which included at least three visits with a dietitian. With the more intensive nutrition intervention, fasting plasma glucose level decreased by 50–100 mg/dl, and the A1C dropped by 1–2%, depending on the duration of diabetes. 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 greater at 1.9% (from 8.8 to 6.9%) [33].

Randomized controlled nutrition therapy outcome studies have documented decreases in A1C of ~1% in newly diagnosed type 1 diabetes [34], 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 who cannot achieve optimal control with MNT and whose disease may be progressing should be prescribed blood glucose-lowering medication, along with additional encouragement to achieve goals of MNT and physical activity [35].

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 (other than insulin) that have become available over the last 5 years. Currently, there are numerous classes of drugs that can be used to initiate or intensify treatment. Each class of drug addresses at least one of the pathophysiologic defects observed in people with type 2 DM. The commonly used medications include insulin sensitizers, insulin secretagogues (glucose dependent and independent), agents that delay the absorption of carbohydrate from the bowel, and those that prevent renal reabsorption of glucose. Insulin sensitizers include the biguanide metformin and thiazolidinediones. Insulin secretagogues include sulfonylureas, non-sulfonylurea secretagogues, GLP-1 agonists, and DPP-4 inhibitors. Alpha glucosidase inhibitors delay the absorption of carbohydrate from the GI tract. Sodium–glucose cotransporter 2 inhibitors prevent renal glucose reabsorption in an insulin-independent manner. 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 wherever possible 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 [5].

Metformin

Metformin is the only biguanide currently in use. 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 association with lactic acidosis in 1976. Metformin improves insulin sensitivity and decreases insulin resistance, targeting a primary defect in type 2 diabetes [36]. 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 [37], which occurs without increased insulin secretion, thus minimizing the risk of hypoglycemia. Metformin also increases glucose utilization by the intestine. Reduction of hepatic glucose production reduces fasting plasma glucose, while the increase in insulin-mediated glucose utilization principally affects postprandial glycemia.

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 Multicenter Metformin 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. $8.6 \pm 0.2\%$) [38]. Metformin also has a favorable effect on weight, which is of considerable importance in the typical type 2 diabetes population

[39]. Maximal efficacy is seen at 12 months, but appears to be sustained for at least 45 months [40].

One major benefit of starting with metformin is that it is one of the few medications 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 [41]. Metformin does not cause hypoglycemia when used as monotherapy and does not increase plasma insulin levels.

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 [42]. 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 by 36%. At 10-year follow-up, significant risk reductions persisted [43].

Additionally, growing evidence suggests that metformin may be associated with decreased risk of cancer and cancer mortality. Several mechanisms of action have been proposed including activation of LKB1/AMPK pathway, induction of cell cycle arrest, inhibition of protein synthesis, reduction in circulating insulin levels, inhibition of the unfolding protein response, activation of the immune system, and eradication of cancer stem cells [44]. A recent meta-analysis of 51 articles, including 1,029,389 patients, found a reduction in the rate of cancer mortality among patients on metformin compared to no metformin with OR 0.65. The risk of any malignancy was decreased as well with OR 0.73. Specific decreases are noted in risk of liver cancer, colorectal cancer, and pancreatic, esophageal, and stomach cancer. No difference was seen in rates of breast cancer [45].

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. The side effects may also enhance 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 [46], possibly in a dose-dependent fashion [47]. 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 [36]. 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 previously approved 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. While prescribing guidelines cite a plasma creatinine of <1.5 mg/dl for men and <1.4 mg/dl for women as contraindications for usage, there is growing evidence that GFR is a better assessment of renal function. A recent systemic review suggests that metformin remains safe with no measurable increase in the risk of lactic acidosis among those patients with mild to moderate chronic kidney disease (GFR 30–60 mL/min) [48]. Most cases of lactic acidosis occur when a condition increasing blood lactate is present, such as hypoxia, hypotension, liver disease, or alcoholism [49] and is not actually related to usage of metformin. A Cochrane review of 347 studies suggests that compared to other treatments for type 2 diabetes, metformin is not associated with any increased risk of lactic acidosis [50]. If metformin is thought to be the cause of the lactic acidosis, the medication can be removed by

hemodialysis. 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 ≥1.5 mg/dl for men and ≥1.4 mg/dl for women or a creatinine clearance <60 ml/min
Age >80 unless creatinine clearance is >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, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, 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. Given that the mechanism of action is through altering gene expression, the onset of action may be slightly delayed though effects appear to be more durable as compared to sulfonylureas. Through PPARs, TZDs act on muscle, liver, and adipose tissue to increase glucose utilization and decrease glucose production. TZDs lower fasting and postprandial glucose and result in a 1.0–1.6% decrement in the A1C [51, 52]. Rates of hypoglycemia are low and comparable to metformin [53].

TZDs initially attracted interest as improvement in insulin sensitivity was thought to modify cardiac risk. TZDs are associated with numerous short-term vascular benefits, including reducing carotid intima-media thickness, endothelial dysfunction, and restenosis after angioplasty [54]. 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 [55]. 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 is no evidence, however, that TZDs improve cardiovascular outcomes in people with diabetes.

There are two TZDs available in the United States, rosiglitazone and pioglitazone, both of which were approved in 1999. Rosiglitazone and pioglitazone can be used as monotherapy or in combination with a variety of other antidiabetes medications, including sulfonylureas, metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, or insulin. However, there are concerns with combined thiazolidinedione and insulin therapy because of an increased incidence of heart failure. This is thought to be due to activation of sodium channels in the distal nephron, which leads to water retention [56].

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 [57]. This redistribution from visceral to

subcutaneous fat is part of the reason that insulin sensitivity increases while weight increases [58].

The use of TZDs has declined for several reasons. In addition to associated weight gain and edema, there has been concern that TZDs increase the incidence of acute coronary events. These concerns were prompted after publication of a meta-analysis showing a 40% increase in risk of MI among patients on rosiglitazone [59]. Another meta-analysis published around the same time 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 [60]. Rosiglitazone in particular was targeted after a meta-analysis reported that the incidence of cardiac events with pioglitazone therapy was significantly less than with rosiglitazone therapy [61]. As a result of these concerns, the FDA implemented a REMS program (risk evaluation and management strategy) in 2011 which severely restricted the prescribing of rosiglitazone. However, in 2013, after data from the RECORD trial confirmed that there was no increased risk of MI or cardiovascular death observed among those patient treated with rosiglitazone, the FDA lifted those restrictions [62]. Unfortunately, because of this controversy, the future of TZDs in clinic practice is unknown. The TOSCA.IT trial, a randomized prospective study evaluating cardiovascular outcomes in patients on combined pioglitazone and metformin therapy compared to sulfonylurea and metformin, may help further clarify some of these concerns [63].

Additional concerns with use of TZD, particularly pioglitazone, revolve around possible increased risk of bladder cancer. An observational cohort study reported a 40% increased risk of bladder cancer among patients using pioglitazone compared to non-pioglitazone users [64]. Similarly, a meta-analysis of 10 studies reported a relative risk of bladder cancer of 1.22 in patients on pioglitazone, but not rosiglitazone [65]. However, more recently published long-term 10-year follow-up from three large database analyses did not show any statistically significant association between pioglitazone use and bladder cancer among 193,099 persons with type 2 diabetes and bladder cancer, so this association remains questionable [66].

There is compelling data that TZD usage may be associated with increased risk of fractures. One of the first studies to describe this was the ADOPT trial (A Diabetes Outcome Progression Trial), a randomized double-blind study comparing rosiglitazone, metformin, and glyburide usage among treatment-naïve type 2 diabetic individuals. This study of 4351 subjects reported approximately twofold increased risk of fracture associated with rosiglitazone use compared to metformin or glyburide. This effect is seen in both pre- and post-menopausal women after 1 year of treatment with rosiglitazone [67]. A meta-analysis of >45,000 subjects from randomized control trials and observational studies showed that TZD use is associated with increased fracture risk compared to control therapies, with an overall odds ratio of 1.45. This risk appears to affect women preferentially, with OR of 2.23 for women using TZDs compared to men with an OR of 1.0 [68]. The observational Health, Aging, and Body Composition Study demonstrated a significant decrease in bone mineral density for each year of TZD use among diabetic women over 70 compared to non-TZD users [69]. This effect may be mediated by TZD activation of PPAR γ receptors, which are found on osteoblasts and osteoclasts [70].

Sulfonylureas

Sulfonylureas (SUs) are a class of commonly prescribed antidiabetic drugs used to increase insulin secretion. 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 "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 [71, 72]. 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 (e.g., 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 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 [73, 74]. Sulfonylurea therapy eventually fails to provide adequate glycemic control in the majority of patients with type 2 diabetes, with a 34% failure rate over 5 years of treatment; this may be related to beta cell apoptosis [40, 75].

There is controversy regarding a potential association between SUs and cardiovascular morbidity [74]. 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 [76]. Because of questions related to methodology, several studies attempted to replicate these results. A retrospective cohort study of 5795 newly diagnosed people with type 2 diabetes from Canada 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 [77]. 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 resulting in more myocardial damage. Glimepiride, a second-generation agent, preferentially binds to the pancreatic beta cell SU receptors compared to other SUs agents which have greater affinity for cardiac receptors and therefore may not have the same cardiac risks, although this has not been proven. SUs carry a black box warning (mandated by the FDA) indicating 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 [73]. There was also no increase in cardiovascular mortality observed in the ADOPT study which compared use of glyburide with metformin and rosiglitazone as monotherapy in people with newly diagnosed type 2 DM [40]. A recent meta-analysis of 20 studies did show higher all-cause and cardiovascular mortality associated with sulfonylurea use, but the authors caution the interpretation of these results given the high heterogeneity of the studies reviewed, with many being non-randomized trials [78].

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, GLP-1 agonists, 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 the

so-called early-phase insulin response. In DM2, mealtime insulin response is delayed and blunted, whereas normally prandial insulin increases rapidly and peaks within 1 h. The loss or attenuation of early-phase insulin secretion in type 2 diabetes results in inadequate insulin suppression of hepatic glucose production [79]. 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 [80].

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 a lower risk of hypoglycemia [81]. The non-SU secretagogues are rapidly absorbed, metabolized primarily by the liver, and more than 90% excreted in bile.

In a head-to-head trial, repaglinide was similar to SUs with regard to glucose-lowering effects [82], with reductions in A1c of 0.7–1.5% [83, 84]. 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 [85]. 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 [86]. 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 the drug 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, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors.

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, which 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% [87]. There is no weight gain or hypoglycemia associated with the medication, which is a considerable advantage [88]. 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 those subjects stopped the drug during year 2 [89]. 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 [90].

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 [91], but a larger meta-analysis found no significant effect on lipids with no effect on morbidity or mortality. There may be a small decrement in

body weight associated with the use of this class of drugs [90].

The Incretin System

With the exception of metformin, one frustration for both patient and physician with the early available therapies is that they cause weight gain, in addition to other adverse effects including hypoglycemia. Thus, there is considerable interest in a novel approach to treating DM2 by employing so-called incretin hormones. Eating triggers the secretion of numerous gut hormones that regulate motility and secretion of pancreatic enzymes and bile and stomach acid. These gut hormones also stimulate insulin secretion in a glucose-dependent manner. The observation that enteral nutrition stimulates more insulin release than parenteral nutrition led to the development of the "incretin concept," suggesting an increase in glucose-stimulated insulin release in the presence of nutrients in the gut [92]. Subsequently, several gut-derived hormones involved in glucose homeostasis were identified, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). GLP-1 agonist are 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 [93]. GLP-1 levels are low in the fasting state and increase soon after eating. Incretin hormone levels decline rapidly though, as they are degraded by the enzyme dipeptidyl peptidase 4 (DPP-4), resulting in a half-life on the order of minutes. GLP-1 receptors are present in multiple 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 level must be >55 mg/dl to produce an effect [94]. There is promising evidence that GLP-1 enhances beta cell survival, which may delay the progression of DM2 [95, 96]. GLP-1 also helps to control blood glucose by inhibiting glucagon secretion, slowing gastric emptying, increasing satiety, and 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 [97]. Obese people have less GLP-1 secretion in response to eating than lean people, and weight loss improves GLP-1 levels [98]. 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 [99].

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 [93]

The number of FDA-approved medications that manipulate the incretin system to modulate blood glucose has expanded rapidly over the past several years. Approved GLP-1 agonists now include exenatide (twice daily and weekly formulations), liraglutide, lixisenatide (Europe only),

albiglutide, and dulaglutide. There are four DPP-4 inhibitors on the market, including sitagliptin, saxagliptin, linagliptin, and alogliptin, with several others under 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 [93]. Exendin-4 has approximately 50% homology to mammalian GLP-1 and thus binds to the GLP-1 receptor. It has the distinct advantage of being DPP-4 degradation resistant. Exenatide BID reduces A1C by about 0.8–1.0% over 30 weeks and is associated with modest weight loss of approximately 1.5–3 kg [100]. The open-label extension study of this drug demonstrated continued weight loss of 4–5 kg after 80 weeks [101]. Once weekly long-acting exenatide was approved in 2012. A 30-week noninferiority trial comparing BID versus weekly exenatide showed a greater reduction in A1c with weekly administration (−1.9% vs. −1.5%), with a greater proportion of patients achieving A1c goal. The side effect profile was also improved in the weekly administration with significantly fewer gastrointestinal side effects, though there was an increase in injection site reactions with the weekly treatment [102].

Liraglutide, a partially DPP-4-resistant GLP-1 analogue, was the second GLP-1 receptor agonist marketed in the United States. Because of a fatty acid substitution which limits degradation [103], liraglutide can be dosed once daily and has a greater impact on reducing A1c than exenatide BID (−1.12% for liraglutide vs. 0.79% for exenatide in a 26-week multinational trial) [104]. Weight loss and side effect profiles did not differ significantly between the groups, with the most common side effect being nausea. The DURATION-6 trial compared liraglutide to weekly exenatide and demonstrated a greater A1c reduction in the liraglutide group (−1.48%) compared to weekly exenatide (−1.28%). Significantly more subjects experienced nausea in the liraglutide group (21% vs. 9% with exenatide), and a higher percentage of patients discontinued liraglutide treatment due to side effects [105]. Further studies suggest that liraglutide may be superior to glargine in A1c lowering effects among patients on metformin and/or sulfonylureas. In this population, an A1c reduction of 1.33% was seen in the liraglutide group compared to 1.01% reduction in the glargine group. Of added benefit, the liraglutide-treated group lost a significant amount of weight, while weight gain was noted in the glargine group [106].

Albiglutide was approved in 2014 as a once weekly treatment. Studies have shown noninferiority compared to glargine [107] but did not meet criteria for noninferiority compared to liraglutide [108]. However, as demonstrated in other studies comparing extended release to daily treatment, the rates of side effects, including nausea, vomiting, and hypoglycemia, were lower in the albiglutide group compared to liraglutide. This makes it an attractive option for those patients who cannot tolerate short-acting GLP-1 agonists due to side effects.

Finally, dulaglutide is the newest agent on the market. This is also administered weekly and has been examined in a series of studies known as the AWARD trials, comparing treatment to exenatide BID, glargine, and liraglutide. Dulaglutide treatment resulted in significantly greater lowering of the A1c at all doses (1.5 mg weekly and 0.75 mg weekly) compared to exenatide BID [109]. Higher doses of dulaglutide (1.5 mg weekly) were also superior to glargine [110] and once daily liraglutide at maximal dose [111].

Side effects are generally gastrointestinal, principally nausea with or without 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 the side effects were seldom severe enough to spur trial withdrawal [112]. There has been concern about a possible link between incretin therapies and pancreatitis due to several post-marketing reports of acute pancreatitis. However, subsequent retrospective observational studies have not demonstrated any

increased risk, and prospective randomized trials have not been performed. Regardless, the FDA recommends that other antidiabetic therapies be considered in patients with a personal history of pancreatitis. There is additional concern of increased risk of medullary thyroid cancer based on animal studies showing an increase in C-cell hyperplasia and cancer in mouse models. Rodents have a greater number of GLP-1 receptors on the thyroid gland compared to humans which may explain this finding, as post-marketing studies have not shown any increased risk in people. Despite this, because of the theoretical risk, GLP-1 analogues are contraindicated in patients with personal or family history of medullary thyroid cancer or MEN2 [113].

DPP-4 Inhibitors

Because the GLP-1 analogues are injectable, there has been considerable interest in oral incretin therapy. There are four medications currently approved in this class: sitagliptin, saxagliptin, linagliptin, and alogliptin. DPP-4 degrades endogenous GLP-1, resulting in a short half-life. The DPP-4 inhibitors block degradation, resulting in prolonged action of endogenous GLP-1. 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 [114]. However, DPP-4 inhibitors are less effective than GLP-1 analogues at lowering A1c, likely because the supratherapeutic level of GLP-1 seen with the use of analogues cannot be achieved biologically by inhibiting breakdown by DPP-4 inhibitors [115]. Additionally, DPP-4 inhibitors appear to be less effective than many oral agents on the market. They have a smaller effect on A1c than metformin and show less improvement in A1c compared to other agents when used as an add-on therapy [116].

Despite limited efficacy, DPP-4 inhibitors may be beneficial for certain patients due to a favorable weight and side effect profile. While DPP-4 inhibitors are not associated with weight loss, these agents are "weight neutral" and are associated with few side effects; notably common side effects of GLP-1 agonists including nausea, vomiting, and delayed gastric emptying are not seen with DPP-4 inhibitors. The risk of hypoglycemia is increased only when these drugs are used in combination with insulin and sulfonylureas.

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 [94]. More recently, there have been several published cases of severe arthropathy associated with treatment with DPP-4 inhibitors. This reaction may also be due to immunomodulatory effects of inhibiting DPP-4, though the exact pathophysiology has not been clearly described. In the majority of cases, symptoms resolved after cessation of the DPP-4 inhibitor and have been described to reoccur after rechallenge of the offending medication [117]. The FDA issued a warning regarding the risk of joint pains in 2015.

SGLT-2 Inhibitors

SGLT-2 inhibitors are the newest class of oral agents available for treating diabetes and have a novel mechanism of action. Canagliflozin was the first agent approved in 2013. Subsequently, dapagliflozin and empagliflozin have also been approved. All of the currently approved medications inhibit the function of the SGLT-2 transporter in the proximal convoluted tubule. This is a high-capacity, low-affinity glucose transporter responsible for 90% of renal glucose reabsorption into circulation [118]. Typical renal filtration of glucose is approximately 180 g/day; however, by inhibiting the SGLT-2 transporter, the renal threshold is lowered, thereby decreasing the absorption of glucose and resulting in significant increases in glycosuria, leading to improvements in plasma blood glucose [119]. This mechanism of

action is completely independent of effects of insulin, making SGLT-2 inhibitors a good option for management regardless of the stage of a patient's diabetes. However, it does necessitate adequate renal filtration, so this class should not be used in patients with GFR <45–60 ml/min/1.73 m^2, depending on the agent of choice [120].

SGLT-2 inhibitors are fairly efficacious and result in 0.7–1.0% A1c reduction when used as monotherapy [121, 122] or add-on therapy [123, 124]. This effect is greater in the setting of poorly controlled diabetes (A1c >10%), with a reduction of 1.9–2.5% in A1c from baseline seen in this subset of patients [121, 122]. Due to their mechanism of action, SGLT-2 inhibitors result in a caloric loss of 200–300 kCal/day. This effect may be responsible for the modest weight loss of 1–5 kg that results from treatment. This weight loss appears to be sustained for up to 1 year of follow-up [125]. This weight loss benefit is seen even when SGLT-2 inhibitors are combined with insulin therapy [126], making these medications an appealing option for overweight or obese patients. Improvements in systolic and diastolic blood pressure are also seen, with mean drop of 3.7 mmHg systolic and 1.75 mmHg diastolic across studies [127]. The EMPA-REG study was a randomized placebo controlled trial evaluating cardiovascular morbidity and mortality in 7020 patients treated with empagliflozin. Compared to placebo, those treated with empagliflozin had significantly lower rates of cardiovascular death, hospitalization for heart failure, and death from any cause [128]. Further studies are underway to understand how empagliflozin might contribute to decreased mortality and clarify if this is a class effect or specific to empagliflozin.

The most common side effect associated with SGLT-2 inhibitor use is a twofold risk of genitourinary infections, including urinary tract infections and mycotic infections, thought to be related to glycosuria [120]. This is more common in women and uncircumcised men, along with those with a prior history of GU infections, so caution should be used when prescribing SGLT-2 inhibitors to people with a history of recurrent infections in the past. Additionally, attention must be paid when administering these medications to patients sensitive to volume shifts and electrolyte disturbances, as osmotic diuresis with increased urination and thirst is common, particularly when used in combination with diuretics [129]. This diuresis can also result in orthostatic hypotension. There have also been reports of elevated potassium levels associated with canagliflozin use. It is unclear if dapagliflozin and empagliflozin are similarly associated with hyperkalemia [130]. Small increases in HDL and LDL are seen, with decreases in triglycerides [127]. However, the clinical significance of this is currently unknown. The risk of hypoglycemia is low except when used in combination with a secretagogue (sulfonylurea or meglitinide) or insulin.

In 2015, the FDA issued a warning of increased risk of euglycemic DKA with the use of SGLT-2 inhibitors. The cause of DKA is thought to be multifactorial. Due to the medication's intended glucosuric effect resulting in lower plasma glucose, insulin doses are often decreased, thereby increasing lipolysis and ketogenesis. There is also suggestion that SGLT-2 inhibitors affect renal handling of ketone bodies and lead to enhanced ketone body reabsorption. Finally, there is evidence that SGLT-2 inhibitors have direct effects on alpha cells and increase glucagon secretion [131]. The clinical significance of this is unclear, as the majority of reported cases have been in patients on insulin with precipitating factors such as infection or non-compliance. An analysis of the canagliflozin type 2 diabetes clinical program data suggested that rates of DKA in the setting of SGLT-2 inhibitor use are low (<0.1%) and similar in frequency to the general population of patients with type 2 diabetes [132]. However, this remains an active area of concern, and some providers are encouraging patient self-monitoring of ketones, particularly during times of illness.

There are recent concerns related to increased risk of bone fractures, specifically with the use of canagliflozin. It has been proposed that this risk is related to increased tubular reabsorption of phosphate. Hyperphosphatemia can then lead to increases in PTH, thereby enhancing bone

resorption, decreasing bone mineral, and increasing fracture risk [133, 134]. This phenomenon has only been described with the use of canagliflozin to date, though research is underway to determine if it could represent a class effect.

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 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 [135]. In terms of glycemic control, pramlintide is moderately effective with A1C decrements of 0.5–0.7% in clinical trials [136]. Adverse effects include nausea and hypoglycemia. Approximately 30% of treated participants in the clinical trials have developed nausea, but this side effect tends to abate with time on therapy [137]. 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 [138]. 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 [139], many patients with type 2 diabetes eventually require insulin therapy. Most oral hypoglycemic agents are less effective with time because of the progressive loss of beta cell function. The exception to this may be SGLT-2 inhibitors, due to their mechanism of action, but there are no long-term studies demonstrating maintenance of effectiveness. We also do not know if incretin mimetics lose efficacy over time. In the UKPDS trial, 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 [140]. Insulin therapy is indicated when adequate glycemic control is not achieved using diet, exercise, and one or more antihyperglycemic 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 reasons. Many patients view the need for insulin as a personal failure or a harbinger of doom. Patients and physicians are often reluctant to start insulin because of concerns about weight gain and hypoglycemia [141]. For these reasons, there is significant clinical inertia, with the mean time to treatment intensification being over 700 days despite A1c above goal [142]. 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 low in patients with type 2 diabetes taking insulin.

Normally, insulin is secreted in a pulsatile manner under basal, unstimulated conditions and in response to meals [143]. 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 guide dosing of exogenous insulin therapy. There are many types of insulin or its analogues available, and the differing pharmacokinetics of these agents can be used to mimic physiologic insulin release via multiple daily injections. The details of the onset and duration of actions of these preparations are detailed elsewhere in this book. Generally, insulin preparations can be grouped by pharmacokinetics: rapid, short, intermediate, and long acting. Longer-acting insulin preparations are used as basal insulin one or two times daily, while short- and rapid-acting preparations are used for mealtime coverage. Premixed insulin preparations 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, a basal (long- or intermediate-acting) insulin preparation is employed to mimic insulin secretion in the fasting and postabsorptive state, and a bolus (rapid- or short-acting) insulin preparation is used at mealtime. The rapid-acting insulin analogues produce less postprandial hypoglycemia than short-acting insulins [144], largely related to duration of action, and are associated with greater improvements in A1c [145]. Long-acting insulin analogues are associated with less hypoglycemia due to a less pronounced peak in insulin action compared to NPH [146].

Premixed insulin, which combines a rapid-acting with intermediate-acting insulin preparation, generally provides good but not excellent control. These insulin formulations are generally given twice daily but are occasionally given three times daily before all meals. Certainly premixed insulin formulations have an advantage over basal insulin alone, given the rapid-acting prandial control, and result in a significantly better reduction in HbA1C [147]. Premixing avoids errors from mixing by the patient in a syringe and reduces the numbers of injections, which is advantageous in certain population groups like the elderly and those with visual or fine-motor impairment [148]. But premixed insulin preparations 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. Because of this limitation in dose titration, A1c improvement is generally greater with basal bolus dosing compared to premix insulin regimens [149].

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 existing regimen. 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% [150]. In various "treat-to-target" trials, once daily basal insulin targeting fasting plasma glucose levels allowed the majority of patients to achieve a HbA1C of less than 7%. In these studies, once daily NPH vs. detemir or NPH vs. glargine was equally efficacious, but NPH was associated with significantly more episodes of hypoglycemia than either of these basal analogues, in particular nocturnal hypoglycemia [151, 152]. Insulin preparations can be combined with metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 analogues. We do not recommend discontinuing oral antihyperglycemic medications when insulin is initiated, since there are synergy and an "insulin-sparing" effect when insulin sensitizers [153], including metformin, are continued. Limiting insulin doses may be helpful in minimizing insulin-related weight gain. However, once prandial insulin is required, the dose of other insulin secretagogues may need to be modified to prevent hypoglycemia.

The ADA and EASD recommend starting with a bedtime intermediate-acting insulin preparation or morning or evening long-acting insulin preparation at 10 units or 0.2 U/kg. This dose should be titrated upward by 2–3 units every 3 days until the morning fasting glucose is at goal (70–130 mg/dl) [5]. While more physicians are using basal 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 reviewed. If the prelunch glucose is elevated, then a rapid-acting insulin analogue should be added at breakfast. If the predinner value is elevated, then NPH could be added at breakfast or a rapid-acting insulin analogue can be added at lunch. If pre-bedtime glucose is elevated, a rapid-acting insulin is needed at dinner. The addition of pre-supper prandial insulin analogue 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. An inhaled form of short-acting insulin, Afrezza, was recently approved for prandial use. Its use is currently reserved for patients without any lung disease who might otherwise decline intensification of treatment due to fear of injections [154].

There is no true "maximal dose" of insulin, although variability of insulin absorption increases with higher doses [155]. 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. In patients with high insulin requirements, several options exist, including U-500 insulin, newly approved glargine U-300 [156], Tresiba (degludec) which is available in U-100 and U-200 concentrations, or short-acting lispro U-200.

Side effects of insulin include weight gain and hypoglycemia. The weight gain associated with insulin can be marked and create a vicious circle of increasing insulin requirements due to increased weight, leading to further weight gain. In the DCCT, mean weight gain after the first year was 3.6 $\pm$ 4.8 kg and 3.0 $\pm$ 4.1 kg for men and women, respectively, with intensive therapy [157]. 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 [73]. Intensive therapy with insulin in the DCCT also caused a relatively high rate of hypoglycemia of 61 per 100 patient-years [158]. 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. Degludec, a recently approved novel ultra-long-acting insulin analogue, may be associated with a more significant decrease in the risk of hypoglycemia, even when compared to other long-acting insulins [159]. Rapid-acting insulin analogues may reduce the risk of hypoglycemia compared with regular insulin [160], 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. 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. 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 can be 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 DPP-4 inhibitor or non-SU secretagogue may make more sense. In an obese patient, a trial with GLP-1 agonists or SGLT-2 inhibitors should be considered. Table 1 summarizes the available therapies as recommended by the ADA and EASD.

Table 1 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)
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, once weekly dosing	GI side effects, expensive
Other therapy α-glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5a	Rapidly effective[a]	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	Expensive, poor efficacy compared to other agents
SGLT-2 inhibitor	0.7–1.0	Weight loss, possible cardiovascular benefit	Genital mycotic infections, possible risk of DKA and bone fractures

[a]Repaglinide more effective in lowering HbA1C than nateglinide
Reproduced from Inzucchi et al. [5]

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