CHAPTER **43**

TYPE 2 DIABETES MELLITUS TREATMENT

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INTRODUCTION

Every podiatric physician is familiar with type 2 diabetes mellitus (T2DM) and its consequences. However, there have been some recent additions to the pharmacologic treatment of T2DM. Additionally, there has been some confusion about the proper nomenclature for diabetes. In this update, the most current nomenclature will be utilized. Type 2 diabetes mellitus (T2DM) will replace non-insulin dependent diabetes mellitus due to the fact that most T2DM patients will at some point in their illness require the use of insulin. The update to follow will be a review of critical aspects of familiar medications and the discussion of some exciting emerging treatments for T2DM.

PATHOPHYSIOLOGY OF DIABETES MELLITUS

While it is beyond the scope of this update to fully cover the pathophysiology of T2DM, a brief summary will be presented. T2DM results from 2 separate but intertwined processes, insulin resistance and ß-cell dysfunction.[1-4] Various environmental and genetic factors play a role in the development of insulin resistance such as aging, obesity, and a decrease in physical activity. The ß-cells of the pancreas will compensate for this resistance early in the disease process by increasing the amount of insulin secreted. Eventually as the ß-cell function decreases, a state of hyperglycemia will develop. According to the United Kingdom Prospective Diabetes Study (UKPDS), a 50% reduction in ß-cell function is present at the time of diagnosis of diabetes.[1-4] The UKPDS study also showed that there is a progressive decline in ß-cell function that continues at a constant rate, regardless of treatment.[1-4] The development of diabetes-related complications, such as neuropathy, retinopathy, and nephropathy, has been shown to correlate with the degree and duration of hyperglycemia.[1,4] Thus, all treatments for T2DM are aimed at returning the patient to a normoglycemic state.[1]

CLASSES OF ANTI-DIABETIC MEDICATION

There are many options for the clinician to choose from in the treatment of T2DM. While there are some differences in the medications within a specific class, each class as a whole will be reviewed.

Sulfonylureas

The first class of hypoglycemic agents that became available were the sulfonylureas (SU). These agents are classified as insulin secretagogues, as they facilitate the release of insulin at lower glucose levels. The SU achieve this by binding to the SU receptor on the ß-cell and inducing a closure of the K-ATP channels leading to cell membrane depolarization and release of insulin. The increased concentrations of insulin lead to a diminished blood glucose level, despite insulin resistance.[3] Generally, SU therapy leads to a decline in the HbA1c level of 1-2%.[2,3] As ß-cell function declines, treatment with a SU will become less effective. In long-term diabetics with poor ß-cell function, SU therapy is likely to be ineffective, making combination or insulin therapy necessary.[5]

The second generation members of this class (glipizide, glyburide, glimepiride) are generally safer with less risk of hypoglycemia when compared with the first generation agents (tolbutamide, chlorpropamide) without a decrease in efficacy. All agents in this class generally result in a weight gain between 2kg and 5kg.[3] The maximal clinical effect is usually seen with half the maximal dosage of these agents; however individual drugs vary in the amount and frequency of dosing. In the UKPDS, subjects treated with SU experienced a 25% reduction in microvascular endpoints (retinopathy, nephropathy, etc.).[3]

Meglitinides

The meglitinides (repaglinide, nateglinide) are also known as rapid-acting prandial insulin releasers or non-SU insulin secretagogues. They were developed to address post-prandial hyperglycemia and have rapid onset and a short duration of action. They bind to the SU receptor and have the same mechanism of action as the SUs. However, they

have much shorter half lives and their duration of action is only about 3 hours. Because of their short duration of action, they have to be dosed 3-times daily immediately prior to meals. The efficacy of the meglitinides is similar to that of the SUs, 1-2% decrease in HgA1c.[3,5]

There is a decreased risk of hypoglycemia with meglitinides when compared with SUs and the weight gain that is observed is less than that caused by SUs. These medications are better suited to patients with erratic meal schedules than the SUs; however, no long-term studies have been conducted to evaluate the risk factor reduction for micro/macrovascular disease.[3,5]

Biguanides

The biguanides have been available internationally for many decades; however, have only been approved in the US since 1995. Currently, metformin is the only available agent as the earlier agents (buformin, phenformin) were associated with an unacceptably high risk of lactic acidosis.[6] Metformin is considered an insulin sensitizing agent, acting mainly at the liver to suppress gluconeogenesis and glycogenolysis. It also stimulates glucose uptake by insulin-sensitive glucose transporters within the skeletal muscle.[5] In general, a decline of 1-2% in the HbA1c can be expected with metformin treatment.[1,5] However, as with the SU, ß-cell function will continue to decline as the disease progresses, making metformin therapy less effective.

Favorable side effects are that metformin is weight-neutral or causes a slight decline in body weight and an improvement in the patient's lipid profile by decreasing LDL and triglycerides.[3] Additionally, in women with polycystic ovarian syndrome metformin has been shown to improve ovulatory function. Perhaps most significantly, metformin may prevent the progression of impaired glucose tolerance (IGT) to T2DM.[3]

Common adverse effects include abdominal pain, nausea, and diarrhea, which commonly resolve by taking metformin with food and slowly titrating the dose upward. More serious complications include lactic acidosis, which occurs in 1 out of 30,000 patients. To reduce this risk, careful patient selection is key. Patients with renal insufficiency, dehydration, hepatic dysfunction, alcoholism, CHF, metabolic acidosis, those undergoing surgery, studies with radio-contrast dyes and patients with acute illnesses should not be given metformin.[1,5]

Glucosidase Inhibitors

The Glucosidase inhibitors (AGIs), which include acarbose and miglitol, are a relatively new class of anti-hyperglycemic agents. They work by inhibiting the breakdown of disaccharides at the brush border in the intestine. This prevents the cleavage of di/oligosaccharides and defers carbohydrate digestion until further along the digestive tract. This delays the absorption of glucose and diminishes the magnitude of the post-prandial hyperglycemia.[3,5] The efficacy of AGIs is less than SUs or metformin (a 0.5-1% reduction in HbA1c). These agents however, do not have as significant of an effect on fasting hyperglycemia as the SUs and metformin and thus are generally used as adjuncts to other therapy.[3]

Despite their inferior efficacy in reduction of the HbA1c, AGIs have the benefits of being nonsystemic and offering a mild reduction in the levels of triglycerides. However, there have been no large studies to examine the risk reduction of diabetic complications with the use of AGIs. The adverse effects of the AGIs include flatulence, abdominal discomfort, and diarrhea. Often the side-effects are severe enough to discontinue therapy.[3,5]

Thiazolidinediones

The thiazolidinediones (TZDs) are new additions into the US market. There are currently 2 members of this class of anti-hyperglycemic agents, pioglitazone (Actos, Takeda Pharmecuticals, Princeton, NJ) and rosiglitazone (Avandia, GlaxoSmithKline, Philadelphia, PA). They act by binding to the peroxisome proliferators activated receptor gamma (PPAR-ß), which is a nuclear receptor that modulates the transcription of insulin-sensitive genes that are involved in the metabolism of lipids and carbohydrates. PPAR-ß is expressed in all tissues; however, adipose tissue has the highest concentrations. As a result of stimulating the PPAR-ß receptors, TZDs increase the glucose uptake in adipocytes as well as in skeletal muscle in addition to suppressing gluconeogenesis in the liver.[5] The TZDs do not act directly on the ß-cells, instead they sensitize the peripheral tissues to the effects of insulin, most notably the adipocytes and myocytes.[3] The TZDs reduce the HbA1c by a similar level as the SUs and metformin (1-2%). Additionally, they improve the lipid profile by increasing HDL, decreasing triglycerides and causing a shift in the LDL to a less atherogenic form.[3,5] There have also been reports that suggest that the use of a TZD may prevent the progression of impaired glucose tolerance to diabetes.[3]

Side effects of the TZDs include peripheral edema, weight-gain, and rarely, anemia. TZDs are contraindicated in patients with liver disease and CHF. While there is an association with TZD use and the development of CHF, recent studies have suggested that there is no increased mortality associated with TZD-induced CHF.[7] Recently there has been literature suggesting that TZDs, primarily

rosiglitazone, may contribute to a decrease in bone mineral density, especially in postmenopausal women, that leads to an increased risk of fracture.[8]

Incretins

An exciting new class of anti-hyperglycemic agents that are emerging are agents that utilize the incretin pathway to achieve anti-hyperglycemic effects. Endogenous incretins are gut peptides that are released in response to the ingestion of food and potentiate post-prandial insulin secretion, the most important of which are glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, GLP-1 and GIP, respectively. These hormones bind to the islet cells and enhance the glucose-induced insulin secretion, which is known as the incretin effect. This effect is most readily visualized by comparing the insulin response to equal doses of glucose give either orally or intravenously. When given orally, the glucose will stimulate a much greater insulin response than the same amount given intravenously. Patients with T2DM tend to be deficient in GLP-1 and resistant to the effects of GIP.[2,9,10]

Currently there are a few incretin-based therapies available. Exenatide (Byetta, Amylin Pharmaceuticals, San Diego) is a synthetic form of exendin-4 which binds to the GLP-1 receptor promotes glucose-dependent insulin secretion, delayed gastric emptying, appetite suppression and inhibition of glucagons secretion. In the Diabetes Management for Improving Glucose Outcomes (AMIGO) trials, exenatide was found to decrease the HbA1c of uncontrolled T2DM patients by 0.7-0.8% over the reduction already achieved with metformin, SU or a combination of both.[2] Exenatide is commonly dosed at 5 or 10 mcg injected subcutaneously twice a day. Exenatide has been shown to result in statistically significant weight-loss, 1.6 kg, in patients with T2DM.[2] The most common side effects were nausea and vomiting, however, there was a 5-36% risk of hypoglycemia with exenatide therapy when combined with other oral hypoglycemic regimens, which was worse when combined with SUs. Additionally, reports of acute renal insufficiency and acute pancreatitis have surfaced in postmarket research.

Another type of medication that acts on the endogenous incretin system are the dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents raise endogenous GLP-1 levels by selectively and reversibly inhibiting DPP-4. There are currently two agents in this class sitagliptin (Januvia, Merck Sharp & Dohme, Whitehouse Station, NJ) and vildagliptin (Galvus, Novartis Pharmaceuticals, Basel, Switzerland). These agents have been shown to decrease the HbA1c by 0.6-1.1% when used as monotherapy and in combination with other oral therapy.[2,10] DPP-4 inhibitors act through endogenous systems and have a side effect profile that is similar to that of a placebo. They are not associated with hypoglycemia, are weight-neutral and are orally dosed either daily (sitagliptin) or twice daily (vildagliptin). These characteristics make DPP-4 inhibitors an attractive alternative to the GLP-1 mimetics.[2,10]

Amylin analogues

Amylin is a hormone that is released by the ß-cells with insulin in response to hyperglycemia.[9] It is believed that amylin binds to amylin receptors in the brain and exerts its effects (delayed gastric emptying and suppression of glucagon secretion) via the vagus nerve.[11] The synthetic analogue Pramlintide (Symlin, a 0.6% reduction in HbA1c levels was observed along with statistically significant weight loss when pramlintide was added to the insulin regimen of patients with uncontrolled T2DM. An increased risk of severe hypoglycemia 3 hours after pramlintide administration with insulin has been reported.[9,10] Additionally, mild-moderate nausea and diarrhea were among the most common side effects. The dosing schedule (subcutaneous injection immediately before meals) and cost ($382/month) are the major limiting factors to the widespread use of pramlintide in the treatment of T2DM.[9]

ALGORITHM FOR TREATMENT OF TYPE 2 DIABETES MELLITUS

While there are a multitude of options for the treatment of T2DM, the cornerstone should be lifestyle modification. Without strict adherence to a sound diet plan, regular exercise, restricting alcohol and cessation of tobacco use, any treatment modality will be doomed to failure and the patient placed at increased risk for the development of diabetes related complications.

Currently, when patients with T2DM are initiated on therapy, metformin is generally the first-line option. It offers proven reduction of a multitude of cardiovascular risk factors, weight loss and improvements in the lipid profile, all without the risk of hypoglycemia. SUs have classically been the first-line treatment in T2DM. They have been extensively studied and have been shown to reduce the risk of diabetic complications. However, with the risk of hypoglycemia and the development of other oral medications that have fewer side effects, SUs are generally added as an adjunctive agent when first-line treatment fails. TZDs are useful for treatment of IGT and early in T2DM. They potentially offer cardiovascular protection as well as being equally efficacious as the SUs and metformin.

If suboptimal glycemic control is achieved with monotherapy, then combination therapy may be considered. The effects of metformin, AGIs, and SUs are additive when they are combined. One must always be cautious with the possibility of hypoglycemia when multiple agents are used. If adequate glyemic control is not achievable when on a combination of multiple oral therapies, then insulin may be added to the patient's regimen.[1,4]

Some of the newer medications that have been suggested to protect ß-cell mass will probably become first-line agents in the management of T2DM. TZDs, DPP-4 inhibitors and exenatide all target specific defects in the metabolism of the T2DM. This may potentially allow for more effective treatment with the least number of side-effects.

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