
Newer Treatment Strategies for the Management of Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus is a multiorgan, metabolic disease associated with multiple microvascular and macrovascular complications. The incidence of type 2 diabetes is growing at an alarming rate. Achieving and maintaining near-normal blood glucose and glycosylated hemoglobin levels (A1C) are of the utmost importance. Existing treatment options for managing type 2 diabetes, which have primarily included

sulfonylureas and biguanides, are insufficient at achieving these treatment goals alone, particularly if used long term. The need to explore newer and better treatment options that provide longer lasting glucose control and at the same time focus on targeting cardiovascular risk factors to minimize and prevent the serious complications associated with this multifaceted disease becomes quite obvious.

KEY WORDS: Type 2 diabetes, A1C, nonpharmacological, pharmacological, algorithm.

INTRODUCTION

Type 2 diabetes mellitus is growing at an alarming epidemic rate, with more than 800,000 Americans diagnosed annually and nearly a 33% increase within the past decade. Historically, people who were diagnosed with type 2 diabetes were older than the age of 40 and commonly had a positive family history. Today, however, older age is not a major risk factor. A 76% increase in type 2 diabetes has been observed in the 30- to 39-year-old age group over the past 10 years, and more and more children are being diagnosed with this disease that is accompanied by multiple microvascular and macrovascular complications.^{1,2} It is not uncommon that patients have fasting blood glucose levels well above 200 mg/dl, postprandial levels greater than 300 mg/dl, and glycosylated hemoglobin (A1C) levels greater than 9.0% at diagnosis. In addition, we now know that diabetes often accompanies other comorbidities, such as dyslipidemia and hypertension, and that the mortality rates from this disease have dramatically increased over the past 10 years.³ This is why it is essential to identify patients at risk of diabetes and to achieve near-normal blood glucose and A1C levels in patients who have already been diagnosed with diabetes.

With the considerable increase in the prevalence of diabetes and its comorbidities, there has also been a substantial increase in the diabetes products in the health care market. Health care providers have seen the growth in the number of new oral antidiabetic agents in

the past 7 to 8 years, as well as insulin products and insulin delivery devices, not to mention the vast increase in new self-monitoring blood glucose (SMBG) systems.³ With this growth in the diabetes industry, it is essential for diabetes practitioners to be up to date and familiar with the various treatment strategies of this complicated disease.

REVIEW OF TYPE 2 DIABETES AND INSULIN RESISTANCE

As previous articles have mentioned, Type 2 diabetes can result from the body's inability to produce a suf-

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efficient quantity and quality of insulin from the β islet cells in the pancreas (a β -cell secretory defect) and, more commonly, the body's inability to use existing glucose in the bloodstream appropriately and respond to normal circulating concentrations of insulin, known as insulin resistance. In question is the longevity of the β -cell function, especially in response to the stress of decreasing insulin sensitivity at the level of the pancreas, liver, adipose tissue, muscle, and other peripheral tissue.³

The majority of patients with type 2 diabetes exhibit insulin resistance; however, not all patients with insulin resistance develop type 2 diabetes. Approximately 25% of people with insulin resistance will develop diabetes, which is mostly due to the subsequent decreased endogenous insulin production.⁴ We also know that by the time a patient is diagnosed with diabetes, the β -cell function is already declining and will steadily continue down this path over time, necessitating exogenous insulin supplementation. In addition, insulin resistance and hyperglycemia are associated with hypertension and lipid abnormalities. Therefore, treatment strategies need to focus on several levels—increasing insulin sensitivity, maintaining appropriate insulin production to overcome the resistance, and reducing the cardiovascular risk factors.⁴

TREATMENT STRATEGIES

Considering the dramatic increase in diabetes and the inability to reduce the morbidity and mortality associated with it, conventional treatment strategies need to be reevaluated.⁵ The focus of treatment in the management of type 2 diabetes needs to be on “fixing the problem” as opposed to treating the symptoms. An important fact for health care providers to keep in mind is that the nonpharmacological treatment strategies are equally, if not more, important than the pharmacological treatment options available.

Nonpharmacological Therapy

Diabetes self-management education (DSME) is the cornerstone in the treatment of diabetes. Knowledge is power, and the more patients know about diabetes and how they can self-manage or control their disease, the better their chances are of minimizing and preventing complications. The ultimate goal of DSME is to empower the patient to be the responsible party in the management of the disease.⁶

The mainstay of DSME is medical nutrition therapy (MNT), also known as diet, and includes physical activity or exercise. Over time, we have observed an in-

crease in obesity that can be directly compared to the increase in the incidence of type 2 diabetes.⁷

The increase in weight in the average American is largely due to the increase in portion of sizes normally consumed. In 1950, an average-size bottle of cola was 6 oz, which used to be considered 1 serving, as compared to the 21-oz, medium-size soft drink served at most fast-food restaurants today. In addition, the diameter of the “normal” dinner plate has grown from 8 inches in 1960 to 12 to 14 inches today.⁷ Second helpings and “super-sizing” are a way of life when it comes to “normal or daily” food consumption today. In addition, no one has or makes the “extra” time for physical activity; with our American “couch potato” mentalities and the addition of so many convenience items that have so nicely paved their way into our daily lifestyles, it is no wonder that the population in the United States is more than 50% overweight!

Patient education on healthy nutrition and activity is an essential component in diabetes treatment. Macronutrients, specifically carbohydrates, can have a direct impact on how high the blood glucose level will go after consumption. A balanced meal should consist of 50% to 55% of the calories from carbohydrates; up to 20% from protein, if normal renal function exists; and the remainder from fat.^{7,8} In addition, it is preferable that patients with diabetes eat every 3 to 4 hours; however, the size of the meal should be reduced. For example, a patient on a 2000-calorie meal plan would ideally have 50% to 55% of the calories come from carbohydrates, which equates to 250 g to 275 g of carbohydrates per day. Because glucose excursions are often the result of an overabundance of carbohydrate grams from a meal, it is preferred to monitor the amount of carbohydrate grams consumed at each meal and divide the total carbohydrate grams over the day. Again, using the above example, an ideal meal plan would consist of a maximum carbohydrate-per-meal goal of 60 g to 75 g and 30 g to 45 g per snack, not to exceed the 250 g to 275 g total per day. Reading food labels and measuring food for appropriate portion sizes are often necessary when educating patients on carbohydrate counting and MNT.⁷⁻⁹

Activity is another mainstay of DSME. Ideally, patients should exercise 30 to 45 minutes 3 to 5 days per week, at a minimum.¹⁰ However, patients often view activity or exercise as aerobic classes in a fitness center where the patrons are sleek and muscle clad. Although this would be beneficial, it is not necessarily the best choice and can be a negative environment to an overweight, out-of-shape person who has diabetes to boot! Endurance or duration of activity can also be threatening to patients; therefore, it is important to clarify that

exercise can be incorporated into their daily lifestyles and that these activities can be cumulative in duration.^{7,10} For example, if a patient takes three 10-minute walks in a day, he or she has a cumulative total of 30 minutes for that day, which meets the exercise goal. Also, some simple lifestyle modifications, such as parking the car at the end of the shopping mall parking lot instead of waiting for the space closest to the entrance and taking stairs in place of elevators, can be very beneficial.

Another important component, and often considered the most important element in the nonpharmacological treatment of diabetes, is SMBG. Patients who monitor their blood glucose levels frequently and on a regular basis often have better control over their diabetes.^{9,11} SMBG meters allow patients to manage their disease by actually seeing the effect of food, specifically carbohydrates; exercise; and medications on their blood glucose levels. If patients test their blood glucose prior to and 2 hours after a meal, they can observe the effect that a specific amount of food has on their blood glucose levels.^{7,8} It is also possible to view the effects that exercise/activity and medications have on blood glucose levels through SMBG.⁹⁻¹¹ Patients who test regularly are the first to identify a problem or concern in their diabetes management on viewing changes within their blood glucose levels. This empowerment assists patients in taking control of their diabetes, as opposed to their diabetes taking control of them.⁶

Pharmacological Therapy

As for pharmacological treatment strategies, there has been a series of advancements in oral agents and insulin preparations over the past decade. Prior to 1995, sulfonylureas were the only class of oral agents that existed, and when glycemic control was lost or not obtained with these agents, insulin was added or substituted.¹¹ These oral agents of yesteryear are now viewed as third- or fourth-line treatment options or add-on therapies since the introduction of newer classes of oral agents that target key organs other than the pancreas, as well as the underlying pathophysiology of the disease.^{5,12}

Currently, there are 5 general classes of oral agents available and several more on the horizon. There are 2 different classes of antidiabetic agents that target the pancreas. They are also referred to as secretagogues (eg, oral sulfonylureas-glyburide) and nonsulfonylurea secretagogues (eg, repaglinide), due to their insulin secretory effect on the β -cell. Biguanides (eg, metformin) are another class of oral agents, which target the liver

and decrease gluconeogenesis. The thiazolidinediones (TZDs) (eg, rosiglitazone) reduce peripheral insulin resistance through enhancement of glucose uptake into muscle and adipose tissue and rejuvenate β -cells. Lastly, the α -glucosidase inhibitors (eg, acarbose) delay the absorption of carbohydrates from the intestinal tract by enzyme inhibition (see Table 1).^{12,13}

Current treatment strategies support the use of TZDs as first-line agents for type 2 diabetes, to reduce blood glucose levels, increase insulin sensitivity, improve lipid abnormalities associated with dyslipidemia, and reduce the decline in β -cell function. TZDs exert their action by binding with peroxisome proliferator-activated receptor- γ (PPAR- γ), a second messenger molecule within the nucleus of the peripheral tissue cells. PPAR- γ stimulation then signals transcription for glucose transport 4 (GLUT-4) molecule production.^{12,14} The more GLUT-4 transporters available, the more glucose molecules are allowed to enter into the cell from the bloodstream, resulting in improved glucose uptake and improved insulin sensitivity. PPAR- γ receptors are most plentiful in muscle, adipose, and vascular tissue, of which muscle is the principal site for insulin resistance.¹²

Another benefit of TZDs is the positive effect on lipoproteins associated with dyslipidemia. Although patients with diabetes may have similar LDL levels as those without diabetes, it is the size and density of the LDL particle that differ.¹⁵⁻¹⁷ Due to the elevated triglyceride levels, often patients with diabetes present with a larger quantity of small, dense LDLs that are more atherosclerotic. TZDs convert these small, dense LDLs to larger, more buoyant particles, thereby stabilizing them and reducing their atherogenicity and increasing HDL levels.¹⁶⁻²⁰

TZDs have also been shown to improve and preserve β -cell function. The β -cell function is believed to be lost due to prolonged exposure to elevated concentrations of free fatty acids. Because TZDs display improvement on the lipoprotein components, there is a reduction in circulating free fatty acids, decreasing stress to the β -cell.¹⁷ Because TZDs' target organ is peripheral tissue opposed to the pancreas, there is no risk of hypoglycemia when used as monotherapy. TZDs reduce fasting and postprandial glucose levels, as well as A1C levels.²¹

Biguanides exert their effects on fixing the problem as opposed to treating the symptoms. Metformin inhibits hepatic glucose production indirectly by enhancing glucose uptake into the peripheral tissue. This agent's target organ is the liver, and the risk of hypoglycemia is eliminated when used as monotherapy.^{12,14,21} Additional benefits of metformin include weight loss and

Table 1
Comparison of the Oral Agents Used in the Treatment of Type 2 Diabetes²¹

Class	Oral Agent	Target Organ	Blood Glucose Reduction; Percentage A1C Reduction	Adverse Reactions	Precautions
Sulfonylurea	Glyburide; Glipizide; Glimepiride; Chlorpropamide; Tobutamide	Pancreas	↓ FBG 50-60 mg/dL; ↓ A1C 1.5-2	Hypoglycemia; weight gain; hyperinsulinemia	Use caution in elderly patients, renal or hepatic impairment
Biguanide	Metformin	Liver	↓ FBG 50-60 mg/dL; ↓ A1C 1.5-2	Diarrhea; metallic taste	Contraindicated if SrCr > 1.5 mg/dl in men; > 1.4 mg/dL in women or if CrCl < 60-75 mL/min; use caution in patients with CHF, renal or hepatic disease
Thiazolidinedione	Rosiglitazone; Pioglitazone	Peripheral tissue	↓ FBG 30-60 g/dL; ↓ A1C 0.8-1.5	Weight gain; edema	Contraindicated if ALT > 2.5 upper limit of normal; use caution in patients with CHF or hepatic disease
Nonsulfonylurea secretagogue	Repaglinide; Nateglinide	Pancreas	↓ PPG 40-50 mg/dL; ↓ A1C 0.4-1.7	Hypoglycemia; weight gain; hyperinsulinemia	Use caution in renal or hepatic impairment
Alpha-glucosidase inhibitor	Acarbose; Miglitol	Intestine	↓ PPG 50 mg/dL; ↓ A1C 1.5-2	Flatulence; diarrhea	Avoid if SrCr > 2.0 mg/dL; avoid in patients with GI disorders

Source: Adapted from Zettervall.

Note: FBG = fasting blood glucose; SrCr = serum creatinine; CrCl = creatinine clearance; CHF = congestive heart failure; ALT = alanine transaminase; PPG = postprandial glucose.

improved lipid profiles, increases in HDL, and decreases in triglycerides and LDL. Other cardiovascular benefits of metformin are its positive effects on clotting factors and platelet function, thereby reducing thrombosis. Metformin reduces fasting glucose and A1C levels.^{12,21} Currently, many health care providers use metformin regularly as a first-line pharmacological treatment for newly diagnosed patients, especially in those who are overweight and/or have concurrent lipid disorders. Nevertheless, more aggressive treatment protocols are suggesting that metformin be used in combination with a TZD as first-line therapy (eg, Avandamet®) or as an adjunct therapy, second line.^{12,22}

Secretagogues (eg, sulfonylureas and nonsulfonylureas) stimulate phase II insulin release from the pancreatic β -cell. Phase II insulin release is insulin secreted in an effort to reduce elevated postprandial blood glucose levels back to normal. However, in patients with type 2 diabetes, phase II insulin production is already elevated, resulting in hyperinsulinemia.^{12,14,21} It is true that nonsulfonylureas have a shorter onset and duration of action when compared to sulfonylureas; nevertheless, both classes of agents stimulate phase II insulin release from β -cells. Both of these classes of oral agents target the pancreas; there-

fore, the risk for hypoglycemia is obvious, although the risk is somewhat less in the nonsulfonylurea secretagogues.^{14,21} Nonsulfonylureas are best used in sulfonylurea-naive patients, and both agents may be considered when blood glucose levels are extremely elevated and/or when other classes of agents are ineffective in lowering blood glucose levels to target range.^{14,21,22} Repaglinide and nateglinide reduce postprandial glucose and A1C levels, whereas sulfonylureas reduce fasting glucose, postprandial glucose, and A1C levels.²¹

Diabetes is a multifaceted, progressive disease, and often pharmacological monotherapy is insufficient to achieve and maintain blood glucose goals. It is therefore necessary to supplement the existing therapy. When choosing combination therapy for diabetes patients, it is important to use agents that target different organs. For example, a TZD that targets peripheral tissue can be added to a biguanide, which targets the liver. However, adding on repaglinide to glyburide, which also targets the pancreas, would not be beneficial.^{12,14}

The prevalence of pancreatic β -cell exhaustion or failure often necessitates the need for introduction to insulin. Although patients and some health care providers view insulin as "the last resort," this is not true.

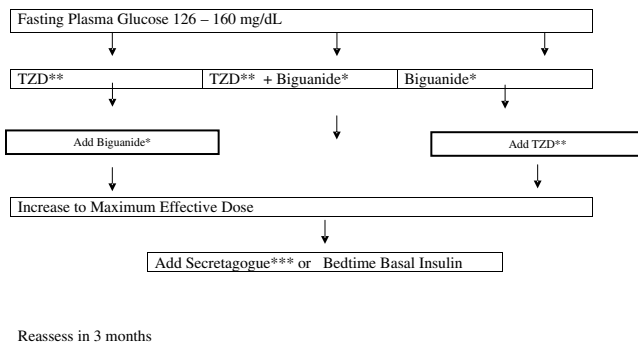


Figure 1. Mild type 2 diabetes mellitus.²²
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- a. Biguanides are contraindicated in patients with renal disease, congestive heart failure, and liver disease.
- b. Thiazolidinediones (TZDs) can cause fluid retention, which may exacerbate or lead to heart failure.
- c. Sulfonylureas may cause hypoglycemia. If hypoglycemia does occur, titrate back or discontinue secretagogue.

Insulin can be beneficial in quickly lowering and achieving blood glucose target goals.^{23,24} The standard rule of thumb when adding insulin to an existing oral regimen is to introduce basal bedtime insulin, such as insulin glargine or NPH.^{23,24} A once-daily injection is often enough to reach blood glucose goals and can lead to a decrease or elimination of one or more of the oral agents currently in the patient's existing treatment regimen. In addition, it is not uncommon when health care providers use insulin instead of a secretagogue in an effort to minimize the risk of β -cell exhaustion.²⁴

ALGORITHM

Diabetes treatment strategies should be individualized to match the needs of each patient, but a general guideline or algorithm may be useful as an initial starting point for management. Recently, proposed algorithms have been established to aid diabetes practitioners in the treatment of their patients with type 2 diabetes (see Figures 1, 2, and 3). These algorithms are based on blood glucose levels and are divided into three categories: mild, moderate, and severe type 2 diabetes.²² Also, pharmacological treatment should be used in combination with nonpharmacological strategies, such as DSME, MNT, activity, and SMBG.

CONCLUSION

With the current national trends leaning toward soaring obesity, diabetes, hypertension, and hyperlipidemia, a serious reevaluation of existing pharmaco-

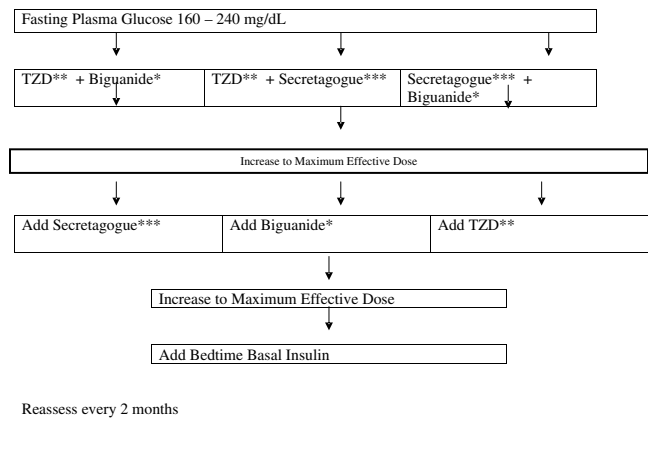


Figure 2. Moderate type 2 diabetes mellitus.²²
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- a. Biguanides are contraindicated in patients with renal disease, congestive heart failure, and liver disease.
- b. Thiazolidinediones (TZDs) can cause fluid retention, which may exacerbate or lead to heart failure.
- c. Sulfonylureas may cause hypoglycemia. If hypoglycemia does occur, titrate back or discontinue secretagogue.

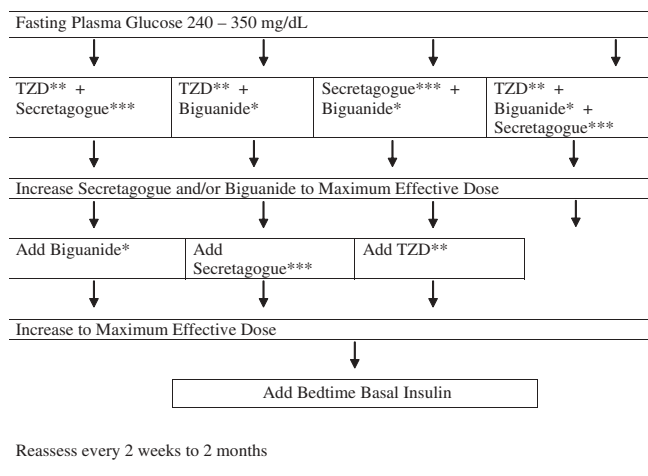


Figure 3. Severe type 2 diabetes mellitus.²²
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- a. Biguanides are contraindicated in patients with renal disease, congestive heart failure, and liver disease.
- b. Thiazolidinediones (TZDs) can cause fluid retention, which may exacerbate or lead to heart failure.
- c. Sulfonylureas may cause hypoglycemia. If hypoglycemia does occur, titrate back or discontinue secretagogue.

logical treatment is imperative. Obtaining near-normal blood glucose levels, A1C levels, blood pressure, and lipid levels needs to be the primary goals of therapy. Because of the complexity of diabetes and its comorbidities, often times multiple agents are necessary to

obtain the various goals of therapy; therefore, patient compliance becomes a serious concern. Treatment strategies that minimize the number of medications and at the same time target the multiple dysfunctions associated with diabetes are obviously preferred. Treatment regimens must attempt to optimize the goals of therapy for type 2 diabetes, yet be easy enough for the person to manage reasonably himself or herself.

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