An Overview of Glycemic Goals and Medications Used to Manage Type 2 Diabetes

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Type 2 diabetes is associated with increased morbidity and mortality, comorbidities, and multiple medication use. Medication regimens may be complex, and adherence to these medications, as well as lifestyle modifications, is an important component to achieving optimal glycemic control. As the number of patients with diabetes increases, becoming familiar with the various treatment options for diabetes will be essential to best serve this patient population. The objectives of this overview are to provide a summary of the current glycemic goals used in monitoring patients with type 2 diabetes and a summary of the medications used in the management of this disease. Nutr Today. 2015;50(1):40–48

It is estimated that 25.8 million people or 8.3% of the US population have diabetes, the seventh leading cause of death in the United States in 2007.[1] Of these 25.8 million people, approximately 7 million are thought to be undiagnosed. In the United States, approximately 5% of adult patients diagnosed with diabetes have type 1 diabetes and 95% of those diagnosed have type 2 diabetes.[2] Nutrition, exercise, and medication all play an important role in the overall management of diabetes. It is important for all members of the healthcare team to be knowledgeable regarding glycemic goals and to be familiar with the medications associated with the treatment of type 2 diabetes.

GLYCEMIC GOALS

Several factors such as hemoglobin A_{1c}, blood glucose values, clinical signs and symptoms, comorbidities, and patient preferences aid practitioners in setting glycemic goals and monitoring patients with diabetes.[3]

Hemoglobin is a complex molecule and is composed of different subunits including hemoglobin A_{1a}, A_{1b}, and A_{1c}.[4] Glucose binds to the hemoglobin A_{1c} portion, and the glycoprotein formed has been found to be elevated in patients with diabetes. Because the life cycle of normal erythrocytes is 120 days, measuring glycated hemoglobin or hemoglobin A_{1c} is considered a good indication of the average glycemic control for the previous 3 months in patients with diabetes and may be utilized to estimate average glucose levels. Patient self-monitoring of blood glucose (SMBG), through preprandial and postprandial blood glucose measurements, is an important addition to A_{1c} and also used in monitoring glycemic control.[3] A_{1c} has less day-to-day variation than SMBG but is difficult to interpret in patients with certain anemias and hemoglobin variants because of interference in the laboratory

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measurement of A_{1c}. Utilizing both SMBG and A_{1c} provides assessment of immediate- and long-term glycemic control.

Table 1 summarizes general glycemic goals from the American Diabetes Association for most adults. For many nonpregnant adult patients, a target A_{1c} goal of less than 7% is acceptable and associated with a decrease in microvascular complications such as retinopathy, which may progress to blindness, and nephropathy which is the leading cause of renal failure in the United States.[3,5,6]

An A_{1c} goal of less than 6.5% may be appropriate for patients with a recent onset of diabetes, those who do not have significant cardiovascular disease, or those who would be expected to have a greater longevity.[3] These patients may benefit from tighter control if they can be managed safely without adverse treatment effects, such as hypoglycemia.

It also may be acceptable to have more relaxed goals, for example, an A_{1c} of less than 8% in certain individuals with multiple medical conditions, comorbid complications such as retinopathy, nephropathy, coronary heart disease, or peripheral arterial disease or in patients with mildly impaired cognition. In those with difficult-to-control diabetes and symptoms of severe hypoglycemia or in patients with a shorter life expectancy due to disease, illness, or age, less strict goals may help to decrease the risk for hypoglycemia and other complications.

A goal A_{1c} of less than 8.5% may be acceptable in older adults with moderately to severely impaired cognition or decreased functional status. It is important to note that many elderly patients remain active and may not have a shorter life expectancy, so less strict goals may not apply to all older patients.

Self-monitoring of blood glucose goals of preprandial and postprandial blood glucose included in Table 1 are less predictive of the long-term complications of diabetes. Monitoring is aimed at lowering the A_{1c} and assisting patients in monitoring drug therapy and preventing hypoglycemia.

Developing an overall therapeutic plan for an individual patient is not a "one-size-fits-all" approach. Appropriate glycemic goals, patient motivation, and involvement in developing an individualized overall diabetic management plan may be key factors in successfully managing this condition.[7]

LIFESTYLE CHANGES

Achieving glycemic control through lifestyle changes is essential and should be implemented in all patients with diabetes. Patients should be educated on the importance of carbohydrate content of their diet, weight control, physical activity, self-monitoring blood glucose, and the management of blood pressure and cholesterol. However, placing medication management on hold to begin lifestyle changes is not appropriate.[8] Patients diagnosed with type 2 diabetes should begin treatment with metformin, if not contraindicated, simultaneously along with lifestyle changes.[3] Patients who present with chronically high levels of A_{1c} (>9%) are unlikely to be successful with monotherapy and may need 2 or more agents to meet their A_{1c} goal.

MEDICATION

The management of diabetes with medication is complex. Many evidence-based guidelines exist that direct clinicians in the choice of medication. The American College of Endocrinology and the American Association of Clinical Endocrinologists provide an algorithm for glycemic control based on 3 broad ranges of A_{1c} levels.[8] The American Diabetes Association provides diabetes management strategies including general pharmacological approaches to initiate and adjust

TABLE 1 Summary of General Adult Glycemic Goals (Excluding Pregnant Patients)[3]

A_{1c}	Population
<6.5%*	Newly diagnosed who are expected to have a long life span, those without significant cardiovascular disease *Adjust goal if patient experiences adverse effects*
<7%	Many adults
<7.5	Aged >65 y who are considered healthy, without cognitive impairment
<8%	Multiple medical conditions, diabetes that is hard to control, decreased expected life span, history of hypoglycemia, cases of advanced retinopathy, nephropathy, coronary heart disease, cerebrovascular or peripheral arterial disease, older adults with impaired cognition
<8.5%	Limited expected life span due to illness or disease states, older adults with moderate to severe impaired cognition
Recommended plasma glucose goals	
Preprandial	70–130 mg/dL
Postprandial	<180 mg/dL

treatment.[3,9] Other organizations have also published guidelines to identify treatment to achieve glycemic goals based on A_{1c} and varying patient attributes.[10,11] The latest recommendations from the American Diabetes Association and the European Association for the Study of Diabetes introduce a patient-centered approach to glycemic control.[12] Here, patient expectations, risk, disease duration, life expectancy, comorbidities, established complications, and a patient support system are integral parts of managing diabetes.

A major challenge in the treatment of patients with type 2 diabetes is the progression of the disease. Pancreatic β cell function deteriorates over time and can necessitate aggressive or intense therapy. Medication management options target pathophysiological causes of type 2 diabetes, processes related to glucose absorption or excretion, and insulin sensitivity. Alongside the benefit, medication treatment may put patients at risk for hypoglycemia, weight gain, or other adverse effects. Table 2 summarizes medications used in the treatment of type 2 diabetes, their estimated reduction in A_{1c}, physiological action, advantages, and considerations by class. There are currently 12 classes of medications including insulin that are approved for the treatment of type 2 diabetes. This includes several new classes introduced over the last few years.

BIGUANIDE

Metformin is the only biguanide available in the United States. It reduces hepatic glucose production to improve insulin sensitivity and is the treatment of choice for type 2 diabetes for those patients in whom it is not contraindicated.[9] As a single therapy, metformin has been shown to reduce mortality when compared with sulfonylureas or insulin and has favorable effects on total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.[13] The expected decrease in A_{1c} from metformin is 1% to 2% without risk of weight gain or hypoglycemia. Dose-related gastrointestinal adverse effects may occur but may be minimized by initiating therapy at a low dose and titrating up to the recommended dose. Metformin may interfere with vitamin B_{12} absorption, and it is recommended that patients on long-term treatment be monitored for B_{12} deficiency.[9,14] Metformin has not been associated with lactic acidosis but carries that risk due to the mechanism of action of the biguanide medication.[15] Lactic acidosis, although rare, is potentially fatal. Patients at risk are those with renal dysfunction, unstable or acute congestive heart failure, hepatic disease, and those undergoing surgery or iodinated contrast dye studies.

SULFONYLUREAS

Sulfonylureas have been used to treat type 2 diabetes for more than 50 years. They stimulate insulin release from the β cells of the pancreas.[16] They are also referred to as insulin secretagogues and reduce A_{1c} similar to metformin.[9] They are available from generic manufacturers and relatively inexpensive. Sulfonylureas are associated with modest weight gain of approximately 2 kg and pose a major risk of hypoglycemia, which may be severe and life threatening. Medication should be started at a low dose, and higher doses should be avoided as the reduction in glucose is almost fully realized at half the maximum dose. Patients require education regarding hypoglycemia and should be encouraged to self-monitor blood glucose. Sulfonylureas require functional β cells and lose their effectiveness as a patient's disease progresses and β cells deteriorate.

MEGLITINIDES OR GLINIDES

Meglitinides are similar to sulfonylureas but stimulate the release of insulin in a more rapid manner, have a shorter duration of action, and require more frequent administration.[9] These agents are taken 15 to 30 minutes prior to the start of a meal and target postprandial glucose. Weight gain is similar to sulfonylureas, but the overall risk of hypoglycemia is lower. Medication is initiated at a low dose and titrated up. Patients should be educated regarding hypoglycemia and encouraged to self-monitor blood glucose. Meglitinides are not used frequently but may be beneficial for those patients with an irregular lifestyle, where meals are unpredictable. Meglitinides are not taken unless a meal is consumed.

THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) improve insulin sensitivity and reduce glucose production. They decrease A_{1c} approximately 0.5% to 1.5% and may have a more sustained effect on glycemic control compared with that of sulfonylureas.[9,16] In the United States, 2 TZDs, pioglitazone and rosiglitazone, are available. However, in 2010, the US Food and Drug Administration restricted the prescribing and dispensing of rosiglitazone because of data that suggested an increase in cardiovascular events.[17] In late 2013, the Food and Drug Administration removed this restriction after review of more recent data that did not show an increased risk of heart attack compared with metformin and sulfonylureas. Pioglitazone is not associated with an increased risk of cardiovascular events and has a favorable effect on lipid profiles. Both TZDs may cause fluid retention and increase the risk of edema, heart failure, and anemia. Careful clinical monitoring is recommended in patients taking TZDs who are at risk of heart failure. Careful monitoring and some caution are also warranted when TZDs are used in combination with insulin because of concerns of increased rates of heart failure.[16] Thiazolidinediones may cause weight gain similar to sulfonylureas. Pioglitazone, but not rosiglitazone, has been associated with an increased risk of bladder cancer.[18] The long-term use of either rosiglitazone or pioglitazone

TABLE 2 Medications Used in the Treatment of Type 2 Diabetes[9,12,16,18,21,23]

Class/Agent	Estimated % Reduction in A_{1c}	Physiological Action	Advantages	Considerations
Biguanides Metformin *Fortamet* *Glucophage* *Glucophage XR* *Riomet* *Glumetza*	1.0–2.0	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Insulin sensitivity	• Weight neutral • Weight loss • No hypoglycemia	• Diarrhea, abdominal cramping • B_{12} deficiency • Monitor renal function
Sulfonylureas Glyburide *Diabeta* *Micronase* Glipizide *Glucotrol* *Glucotrol XL* Glimepiride *Amaryl*	1.0–2.0	• ↑ Insulin secretion	• ↓Microvascular risk	• Hypoglycemia • Weight gain • Glyburide is not recommended in geriatric patients
Meglitinides Repaglinide *Prandin* Nateglinide *Starlix*	1.0–2.0	• ↑ Insulin secretion	• ↓ Postprandial glucose • Flexible dosing	• Hypoglycemia • Weight gain • Dietary intake of grapefruit juice should remain consistent while on repaglinide
Thiazolidinediones Pioglitazone *Actos* Rosiglitazone *Avandia*	0.5–1.5	• ↑ Insulin sensitivity	• No hypoglycemia • ↑ High-density lipoprotein cholesterol • ↓ Triglycerides	• Weight gain • Edema • Heart failure • Monitor liver function
a-Glucosidase Inhibitors Acarbose *Precose* Miglitol *Glyset*	0.5–1.0	• Slows intestinal carbohydrate digestion and absorption	• Weight neutral • No hypoglycemia	• Frequent dosing • Diarrhea, flatulence
Amylin analogue Pramlintide *Symlin*	0.2–0.4	• Delays gastric • Emptying time • ↓ Glucagon secretion	• Promotes satiety • Decreases appetite	• Nausea, vomiting • Abdominal pain • Anorexia • Hypoglycemia with concomitant insulin • Frequent dosing
DPP-IV inhibitors Alogliptin *Nesina* Saxagliptin *Onglyza* Sitagliptin *Januvia* Linagliptin *Tradjenta*	0.5–0.8	• ↑ Incretins and insulin in a glucose dependent manner • ↓ Glucagon	• ↓ Hypoglycemia • Weight neutral	• Urticaria • Angioedema • Pancreatitis

(continues)

TABLE 2 Medications Used in the Treatment of Type 2 Diabetes[9,12,16,18,21,23], Continued

Class/Agent	Estimated % Reduction in A_{1c}	Physiological Action	Advantages	Considerations
Glucagon-like peptide 1 receptor agonists Albiglutide *Tanzeum* Exenatide *Byetta* *Bydureon* Liraglutide *Victoza*	0.8–1.9	• ↑ Insulin secretion	• ↓ Hypoglycemia	• Nausea, vomiting
Sodium-glucose cotransporter 2 inhibitors Canagliflozin *Invokana* Dapagliflozin *Farxiga*		• ↓ Reabsorption of filtered glucose • ↑ Urinary glucose excretion	• Weight loss • ↓ Hypoglycemia • ↓ Systolic blood pressure	• Osmotic diuresis • Dizziness • Syncope • Hyperkalemia in renal impairment • Genital mycotic infections Urinary tract infections
Bile acid sequestrant Colesevelam *Welchol*	0.5	• Unknown • May ↓ hepatic glucose production • May ↑ incretin levels	• No hypoglycemia • ↓ Low-density lipoprotein cholesterol	• Constipation • ↑ Triglycerides • May ↓ absorption of medications
Dopamine 2 Agonist Bromocriptine *Cycloset*	0.5	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia	• Dizziness • Syncope • Nausea • Fatigue • Rhinitis
Insulin	1.0–2.5	• ↓ Hepatic glucose production • ↓ Lipolysis, proteolysis	• ↑ Effectiveness	• Weight gain • Hypoglycemia

Alogliptin, glipizide, glyburide, linagliptin, pioglitazone, repaglinide, rosiglitazone, saxagliptin, and sitagliptin are also available in combination tablets with metformin. Alogliptin, glimepiride, and metformin are also available in combination tablets with pioglitazone. Glimepiride and metformin are also available in combination tablets with rosiglitazone.

may increase the risk of bone fracture in women with type 2 diabetes.[19] It is important to note, that unlike other antidiabetic agents, these agents may take several weeks for improvement in blood sugars to be appreciated and 2 to 3 months for maximal effect.[16]

α-GLUCOSIDASE INHIBITORS

Inhibiting α-glucosidase enzymes in the small intestine slows the rate of carbohydrate digestion and targets postprandial hyperglycemia. Inhibitors of α-glucosidase yield a small decrease in A_{1c} of 0.5% to 0.8% and do not produce hypoglycemia.[9] They are used less frequently and are poorly tolerated because of a high incidence of dose-dependent gastrointestinal adverse effects. Inhibitors of α-glucosidase need to be dosed frequently, at the start of each meal, are weight neutral, and should be used with caution in patients with chronic intestinal disease.

AMYLIN AGONIST

Amylin is a hormone released with insulin from the pancreas. Amylin suppresses glucagon secretion, delays gastric emptying, and decreases appetite. Pramlintide is an injectable amylin analog that targets postprandial hyperglycemia in type 1 or type 2 diabetes. The reduction of A_{1c} is generally small, 0.2% to 0.4%, although pramlintide works slightly better in patients with A_{1c} levels of greater than 8.5%, providing a modest reduction in A_{1c} of 0.5% to 0.7%.[9,20] A mean weight loss of approximately 0.4 to 1.3 kg over 13 to 26 weeks is associated with use.[20] The net change in weight diminishes over time and may be regained in long-term use. Nausea

and mild to moderate hypoglycemia are the most common adverse effects and reasons for withdrawal of the medication in patients with type 2 diabetes using insulin. Nausea, vomiting, and reduced appetite are common adverse effects of pramlintide. It is relatively expensive, is dosed prior to meals, and requires multiple injections per day and the reduction of meal time insulin doses.

DIPEPTIDYL PEPTIDASE 4 INHIBITORS

Dipeptidyl peptidase 4 (DPP-4) is an endogenous enzyme that breaks down glucagon-like peptide 1 (GLP-1). Dipeptidyl peptidase 4 inhibitors enhance the effect of endogenous GLP-1 described below. They reduce A_{1c} by 0.6% to 0.9%, have a low risk of hypoglycemia, and are weight neutral.[9] Serious allergic and dermatologic reactions have occurred as well as case reports of pancreatitis in patients taking DPP-4 inhibitors.[21] Nasopharyngitis and upper respiratory tract infections may occur with use, but fewer gastrointestinal adverse effects are seen compared with GLP-1 agonists. They are generally well-tolerated oral medications but are relatively expensive.

GLUCAGON-LIKE PEPTIDE 1 AGONISTS

Glucagon-like peptide 1 is an endogenous hormone that stimulates insulin secretion and decreases glucagon secretion. Synthetic GLP-1 agonists are injectable agents that may stimulate insulin secretion from the β cells of the pancreas and reduce glucagon secretion, as well as slow gastric-emptying time and suppress appetite.[22] Glucagon-like peptide 1 agonists reduce A_{1c} 0.8% to 1.9% and may result in modest to significant weight loss. Overweight or obese patients with type 2 diabetes may achieve an average weight loss of 2.8 kg on GLP-1 agonists. There is a high incidence of gastrointestinal disturbances with the use of these agents; nausea is the most frequent and limiting adverse effect but diminishes over time. There is a low risk of hypoglycemia, a mild improvement of blood pressure and fasting lipids, and the possibility of an increased risk of pancreatitis. Glucagon-like peptide 1 agonists are administered subcutaneously and are relatively expensive, a factor that may limit their use in some patients. The most recently approved GLP-1 agonist, albiglutide, is long acting and resists degradation of endogenous DPP-4, allowing for once weekly administration.[23]

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

Canagliflozin and dapagliflozin are newer agents approved for the treatment of type 2 diabetes. Both belong to a class of sodium glucose cotransporter 2 (SGLT2) inhibitors and work by decreasing glucose reabsorption in the proximal tubule. This results in an increased urinary excretion of glucose and decrease in hyperglycemia.[24] Sodium glucose cotransporter 2 inhibitors have beneficial effects on fasting blood glucose and A_{1c}, systolic blood pressure, and body weight. Canagliflozin reduced A_{1c} an average of 0.8% to 1.1%.[25,26] Canagliflozin is associated with an average weight loss of 1.9 to 3.9 kg. Dapagliflozin reduced A_{1c} an average of 0.58% to 0.89% and body weight an average of 2.8 to 3.3 kg.[27] Both SGLT2 inhibitors are associated with a low risk of hypoglycemia.[24] Adverse effects include volume depletion and associated hypotension, syncope, and dizziness, genital mycotic infections, and urinary tract infections. They are not recommended in patients with moderate to severe renal impairment, and caution is warranted in patients at risk for volume depletion, hypotension, and electrolyte disturbances. More studies are needed to assess long-term effects on cardiovascular events and incidences of cancer.

BILE ACID SEQUESTRANT

Colesevelam is a bile acid sequestrant used in the treatment of hyperlipidemia and approved in the United States as adjunctive treatment of type 2 diabetes to improve glycemic control.[28] When given with other antidiabetic agents such as metformin, sulfonylureas, or insulin, coleselvelam reduces A_{1c} an average of 0.5% and improves fasting blood glucose with a low risk of hypoglycemia.[29] Constipation and dyspepsia are the most predominant adverse effects, otherwise well tolerated. Treatment with colesevelam may also increase triglyceride levels; decrease the absorption of fat-soluble vitamins A, D, E, and K; and decrease the absorption of some medications. Colesevelam is not recommended for patients with hypertriglyceridemia or at risk for bowel obstruction and should be given at least 4 hours after administration of medications known to bind to it or medications that have not been studied with it. Colesevelam is not used frequently; it is available only as a branded medication and therefore may be costly. The dual benefit of reducing low-density lipoprotein cholesterol and A_{1c} makes colesevelam a useful add-on for patients with type 2 diabetes.

DOPAMINE 2 AGONISTS

Bromocriptine is a dopamine 2 agonist that has typically been used as an adjunct treatment in Parkinson disease and to treat conditions associated with hyperprolactinemia. A quick release formulation of bromocriptine was approved as an adjunct to diet and exercise to improve glucose control in patients with type 2 diabetes.[30] It is given within 2 hours of awakening and works centrally to stimulate dopamine, restore circadian rhythm, and improve insulin resistance.[31] Hypoglycemia is rare, and treatment results in a modest reduction of A_{1c} of 0.6% to 0.7%. The most common

adverse effects are considered mild and include nausea, rhinitis, constipation, fatigue, vomiting, headache, and dizziness.[30] They usually occur with initial treatment and may be transient. The bromocriptine formulation for type 2 diabetes is reserved as add-on therapy and is available only as a branded medication and therefore may be costly.

INSULIN

Many patients are hesitant when injectable therapy is offered, but insulin may be used successfully as an add-on therapy in type 2 diabetes and is recommended in patients who fail oral medications.[12,32] Many different human insulin analogs exist, and they differ in medication onset, peak, and duration. Table 3 summarizes available insulin agents along with their onset, peak, and duration of action. When warranted, a single daily dose of long-acting, or basal, insulin is recommended in type 2 diabetes. It is a convenient regimen, and daily doses are titrated in small increments according to fasting blood glucose. Once a daily dose is stabilized, introduction to a rapid-acting or short-acting insulin at 1 or more meals or switching to a mixed insulin may be considered to address elevations in postprandial glucose. Multiple insulin regimens

TABLE 3 Insulin Preparations[33]

Type of Insulin	Insulin	Onset	Peak	Duration
Rapid Acting	Inhaled Insulin *Afrezza*	15–30 min	30–60 min min	2–3 h
	Insulin lispro *Humalog*	15–30 min	30 min	3–6.5 h
	Insulin aspart *Novolog*	10–20 min	40–50 min	3–5 h
	Insulin glulisine *Apidra*	25 min	45–48 min	4–5.3 h
Short Acting[a] (Regular)	Human insulin *Humulin R, Novolin R*	30–60 min	2.5–5 h	8–12 h
Intermediate Acting (NPH)	Human insulin *Humulin N Novolin N*	1–4 h	4–14 h	Up to 24 h
Long Acting	Glargine *Lantus*	1.5 h	Without significant peak	24 h
	Detemir *Levemir*	3–4 h	Without significant peak	Up to 24 h
Premixed insulin				
70% NPH +30% Regular *Humulin 70/30 Novolin 70/30*		~30 min	1–3 h	Up to 24 h
70% Aspart Protamine/40% Insulin Aspart *Novolog Mix 70/30*		10–20 min	3.3–4.4 h	Up to 24 h
75% Lispro Protamine/25% Lispro *Humalog Mix 75/25*		15–30 min	2.3–6 h	Up to 24 h
50% Lispro protamine/50% Lispro *Humalog Mix 50/50*		15–30 min	2.3–2.6 h	≥24 h

[a]Short-acting insulin is available in 2 concentrations; 100 U/mL (U100) and 500 U/mL (U500).

exist, and a regimen should be chosen based on an individual patient's needs. Insulin will lower glucose, and doses may be adjusted to reduce A_{1c} to target. Patients on insulin require education regarding signs, symptoms, and management of hypoglycemia and should be encouraged to self-monitor blood glucose. In type 2 diabetes, insulins are most commonly associated with weight gain and a risk of hypoglycemia. Metformin, as well as other agents, may be combined with insulin therapy. Ideal combination therapy utilizes pharmacologic properties that are complementary to each other. The benefits and risks of combining other agents with insulin need to be considered, particularly the increased risk of hypoglycemia and weight gain with sulfonylureas and heart failure and edema with TZDs.

CONCLUSION

Type 2 diabetes is associated with increased morbidity and mortality, comorbidities, and multiple medication use. Medication regimens may be complex, and adherence to these medications, as well as lifestyle modifications, is an important component to achieving optimal glycemic control. As more patients develop diabetes, being familiar with the various treatment options for diabetes is essential to best serve this patient population. The management of diabetes involves a team approach of healthcare practitioners working alongside the patient to develop a personalized therapeutic plan that best benefits and fits the needs of the patient. The therapeutic plan should be continuously evaluated and adjusted when needed.

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