

Medical Treatment of Diabetes Mellitus

Mario Skugor, MD

Department of Endocrinology, Diabetes, and Metabolism
Cleveland Clinic

In the United States, 57.9% of patients with diabetes mellitus (DM) have at least 1 diabetes-related complication and 14.3% of patients with diabetes have 3 or more diabetes-related complications.¹ Achieving glycemic control in patients with DM reduces the development and progression of retinopathy, nephropathy, and neuropathy. Aggressive treatment of dyslipidemia and hypertension decreases macrovascular complications.^{2–4} The techniques for monitoring blood glucose and the various treatment options available to manage glycemic control in patients with diabetes are reviewed below.

Measuring Glycemic Control

The primary techniques available to assess the quality of a patient's glycemic control are self-monitoring of blood glucose and interval measurement of hemoglobin A1c (HbA1c). Continuous glucose monitoring is also available and may be appropriate for select patients, such as patients with brittle diabetes and those using insulin pumps.

Self-monitoring of blood glucose

For patients with type 1 DM and patients with insulin-dependent type 2 DM, self-monitoring of blood glucose allows patients to adjust insulin dosing to prevent hypoglycemia and hyperglycemia.^{2,5–7} The American Diabetes Association (ADA) guidelines recommend that patients with type 1 DM self-monitor their glucose:

- Before eating
- At bedtime
- Before exercise
- If hypoglycemia is suspected
- Until hypoglycemia is corrected

- Postprandially upon occasion
- And before critical tasks (ie, driving).⁸

Patients should be educated about how to use real-time blood glucose values to adjust their food intake and medical therapy.

It is commonly recommended that patients with type 2 DM self-monitor their blood glucose levels, but the evidence to support the effectiveness of this practice is inconclusive. Initial studies showed reductions in HbA1c with self-monitoring; however, the inclusion of beneficial health behaviors such as diet and exercise in the analyses makes it difficult to assess the effectiveness of self-monitor blood glucose alone.^{2,9}

The ADA recommends that nonpregnant adults maintain blood glucose levels of 80 mg/dL to 130 mg/dL preprandial and less than 180 mg/dL postprandial.⁸ The blood glucose goals for patients with gestational diabetes are 95 mg/dL or less preprandial and either 140 mg/dL or less 1-hour postprandial or 120 mg/dL or less 2-hours postprandial.

HbA1c

HbA1c tests reflect the mean blood glucose values over a 3-month period and can predict patients' risk of microvascular complications.^{10,11} The ADA recommends that patients with stable glycemic control have an HbA1c test at least twice a year. Quarterly HbA1c testing is suggested for patients with a recent change in therapy or for patients not meeting their glycemic goals.⁸

Measurement of HbA1c is influenced by the red blood cell turnover rate; therefore, anemia, transfusions, and hemoglobinopathies can cause inaccurate test values. The ADA recommends that nonpregnant adults maintain HbA1c levels near 7%. For patients with diabetes who become pregnant, the goal is HbA1c levels less than 6.0%.⁸ The ADA also recommends that select patients, especially those with a long life expectancy and little comorbidity, adopt glycemic targets near normal levels (HbA1c < 6.5%), providing the target can be achieved without significant hypoglycemia.⁸

Dr. Skugor reported no financial interests or relationships that pose a potential conflict of interest with this article.

doi:10.3949/ccjm.84.s1.07

TABLE 1
Glycemic treatments by therapeutic category

Insulin sensitizers

Biguanide: metformin (Fortamet, Glucophage, Glumetza, Riomet)
Thiazolidinedione: pioglitazone (Actos), rosiglitazone (Avandia)

Insulin secretagogues

Sulfonylureas: chlorpropamide (Diabinese), glimepiride (Amaryl), glipizide (Glucotrol), glyburide (Micronase, Glynase)
Glinides: repaglinide (Prandin), nateglinide (Starlix)

Alpha-glucosidase inhibitors

Acarbose (Precose), miglitol (Glyset), voglibose

Incretin-based therapies

Glucagon-like peptide-1 agonists: albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Bydureon, Byetta), liraglutide (Saxenda, Victoza), lixisenatide (Adlyxin)
Dipeptidyl peptidase-4 inhibitors: alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), sitagliptin (Januvia)

Sodium-glucose transporter-2 inhibitors

Canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance)

Amylinomimetic

Pramlintide (SymlinPen 120, SymlinPen 60)

Dopamine agonist

Bromocriptine (Cycloset)

Insulin

Rapid-acting

Aspart insulin (Novolog)
Glulisine insulin (Apidra)
Lispro insulin (Humalog)

Short-acting

Regular insulin (Humulin R, Humulin R U-500 KwikPen, NovoLIN R, NovoLIN R ReliOn)

Intermediate-acting

Isophane insulin, NPH insulin (Humulin N, Novolin N)

Long-acting

Detemir insulin (Levemir)
Glargine insulin (Basaglar KwikPen, Lantus, Lantus SoloStar, Toujeo SoloStar)
Degludec insulin (Tresiba)

Premixed

Several types intermediate-acting and short-acting insulin combined are available

Based on information from the American Diabetes Association⁸ and Inzucchi et al.¹²

Glycemic Treatment

Treatment options to control blood glucose include insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, incretin-based therapies, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, amylinomimetics (pramlintide), dopamine-receptor agonists (bromocriptine), and insulin (Table 1).^{8,12}

Insulin sensitizers

Biguanides (metformin)

Metformin is the only available biguanide. Metformin should be used as a first-line therapy in patients with type 2 DM whenever possible.¹³ Metformin suppresses hepatic glucose output and primarily affects fasting glycemia; however, reduced postprandial glucose concentrations also occur.

The most common side effects of metformin are diarrhea, nausea, and abdominal discomfort. Metformin has the potential to produce very rare but life-threatening lactic acidosis

(< 1 in 100,000). The use of metformin is contraindicated in patients with a glomerular filtration rate less than 30 mL/min, with acidosis, hypoxia, or dehydration.⁸

Metformin usually does not lead to hypoglycemia when used as monotherapy. It can lead to weight loss (3%–5% of body weight), and it has been shown to decrease plasma triglyceride concentrations (10%–20%).^{8,14,15}

Thiazolidinediones

Thiazolidinediones (TZDs) primarily enhance the insulin sensitivity of muscle and fat tissue and mildly enhance insulin sensitivity of the liver. TZDs lower fasting and postprandial blood glucose levels.

Major side effects of TZDs include weight gain, with an increase in subcutaneous adiposity, and fluid retention. Fluid retention typically manifests as peripheral edema, but heart failure can occur on occasion. These agents should be avoided in patients with functional class III or IV heart failure. The PRO-active trial of the TZD pioglitazone found that pioglitazone did

not increase cardiovascular risk compared with placebo.¹⁶ TZDs have been associated with an increased risk of fractures, particularly in women. When used as monotherapy, TZDs do not cause hypoglycemia. Pioglitazone lowers triglyceride levels, increases high-density lipoprotein cholesterol, and increases the low-density lipoprotein cholesterol particle size.^{8,16–18}

Insulin secretagogues

Insulin secretagogues such as sulfonylureas and glinides stimulate secretion of insulin from the pancreas regardless of the ambient glucose concentration.

Sulfonylureas

Sulfonylureas lower fasting and postprandial glucose levels. The main side effects include weight gain (about 2 kg upon initiation) and hypoglycemia. The UK Prospective Diabetes Study (UKPDS) trial showed a decrease in microvascular complications with the use of sulfonylureas.¹⁹ Caution should be used in patients with liver or kidney dysfunction or patients who frequently skip meals. Newer, second-generation sulfonylureas (ie, glipizide and glimepiride) may have less risk of hypoglycemia because their action is somewhat glucose dependent.^{8,17,19}

Glinides

Glinides, which include repaglinide and nateglenide, have a rapid onset of action and a short duration of action, so they are a good option for patients with erratically timed meals. Glinides have a lower risk of hypoglycemia than sulfonylureas. Caution must be used with glinides in patients with liver dysfunction. Dosing is immediately before meals.^{8,17}

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose, miglitol, and voglibose block the enzyme alpha-glucosidase in the cells of the brush border of the small intestine, which delays absorption of carbohydrates. Alpha-glucosidase inhibitors primarily affect postprandial hyperglycemia without causing hypoglycemia. Abdominal cramps, bloating, flatulence, and diarrhea are the most common side effects. Use of alpha-glucosidase inhibitors should be avoided in patients with severe hepatic or renal impairment. Dosing is prior to carbohydrate-containing meals.^{8,20}

Incretin-based therapies

Therapies that target the incretin hormones to increase insulin production include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

GLP-1 agonists

Exenatide, liraglutide, albiglutide, and dulaglutide are synthetic analogs of the GLP-1 hormone. GLP-1 is produced in the small

intestine; it stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. It also delays gastric emptying and suppresses appetite through central pathways. GLP-1 agonists primarily decrease postprandial blood glucose levels; however, a moderate reduction in fasting blood glucose and some weight loss can also occur.

The major side effects are gastrointestinal complaints such as nausea, vomiting, and diarrhea. Hypoglycemia does not occur unless GLP-1 analogues are combined with a sulfonylurea or insulin. There is a slightly increased risk of acute pancreatitis in patients using GLP-1 agonist medications, and patients must be warned to discontinue use of these medications if abdominal pain occurs.

Dosing of GLP-1 agonist medications is either twice daily, daily, or weekly by subcutaneous injection.^{8,21}

DPP-4 inhibitors

DPP-4 is an enzyme that rapidly degrades GLP-1. Suppression of DPP-4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.

The DPP-4 inhibitors such as linagliptin, sitagliptin, saxagliptin, and alogliptin are given orally once daily. An increased risk of acute pancreatitis has been reported in some patients. Dose reduction is needed in patients with renal impairment for most of these medications.^{8,22}

SGLT-2 inhibitors

SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin and are the newest group of antidiabetic medications. These medications inhibit glucose reabsorption in proximal tubule of the kidney leading to glycosuria, which lowers the blood glucose concentration, lowers blood pressure, and leads to some weight loss. Empagliflozin was shown to be cardioprotective in some patients.²³

SGLT-2 inhibitors are given once a day in the morning and the primary side effects are polyuria and genital yeast infections. These medications are contraindicated in patients with severe end-stage renal disease and those who are on dialysis.^{8,24}

Pramlintide (amylinomimetics)

Pramlintide, an amylinomimetic, is a synthetic drug that acts like amylin, a hormone secreted by beta cells that suppresses glucagon secretion, slows gastric emptying, and suppresses appetite through central pathways. Pramlintide acts primarily on postprandial blood glucose levels.

The side effects of pramlintide are gastrointestinal complaints, especially nausea. Currently, pramlintide is approved only as an adjunctive therapy with insulin, and it can be used in patients with type 1 DM or type 2 DM. The dose for type 1

DM is 15 µg before each meal subcutaneously, and for type 2 DM it is generally 60 µg before meals.²⁵

Dopamine-receptor agonist (bromocriptine)

Bromocriptine is a central dopamine-receptor agonist, and when given in rapid-release form within 2 hours of awakening in the morning, it improves glycemic control for patients with type 2 DM. The mechanism of action resulting in improved glycemic control is unknown. Studies have demonstrated the cardiovascular safety of bromocriptine.²⁶

Side effects of bromocriptine include hypotension, somnolence, and nausea. Individuals with psychiatric disorders may experience exacerbation while taking bromocriptine. Bromocriptine is taken with food to diminish nausea.²⁷

Insulin

Insulin and insulin analogues remain the most direct method of reducing hyperglycemia. There is no upper limit in dosing for therapeutic effect, so it can be used to bring any HbA1c down to near-normal levels. Other benefits of insulin include reducing triglyceride levels and increasing high-density lipoprotein cholesterol.

Hypoglycemia is a concern with use of insulin, and studies have shown that episodes for which the patient required assistance due to the hypoglycemia occurred between 1 and 3 times per 100 patient-years.¹³ Weight gain can occur after initiation of insulin therapy, and patients typically gain 2 kg to 4 kg.⁸

Initiation and Titration of Therapy

All patients with type 1 DM require insulin therapy. There are 2 regimens available: basal-bolus and insulin-pump therapy. Patients with type 2 DM often require insulin, which can be combined with oral hypoglycemic agents. Regimens include basal insulin only, twice-daily premixed insulin, basal-bolus therapy, and insulin-pump therapy.²⁸

Basal-bolus therapy

The basal-bolus regimen combines a long-acting agent for basal-insulin needs that is used once or twice daily and a rapid-acting agent for prandial coverage. Traditionally, 50% of the total daily dose is given as basal insulin (detemir, glargine, degludec) and the remaining dose as prandial insulin divided equally before meals (regular, lispro, glulisine, or aspart).

The meal dose of insulin can be fixed, but it is better to determine the dose based on the carbohydrate content of the meal. To do so, patients should be educated about carbohydrate counting and the dose of insulin required to cover the carbohydrate content of the meal. Consultation with a diabe-

tes educator is needed for patients to effectively dose insulin based on the carbohydrate content of meals. Patients are also provided with a sliding scale of supplemental insulin to use as a third component of therapy when the blood glucose level is higher than desired.

The starting total daily insulin dose is typically 0.3 U/kg for patients with type 1 DM and 0.5 U/kg for patients with type 2 DM if no other medications are used. The ADA recommends adding basal insulin at 0.1 to 0.2 U/kg for patients with type 2 DM once they need it. The key to good glycemic control is self-monitoring of blood glucose by the patient and frequent adjustment of the regimen until control is achieved.⁸

Insulin-pump therapy

The insulin pump allows the use of different basal insulin rates at different periods of the day for greater flexibility with daily dosing. The insulin pump also allows administration of the meal bolus as a single discrete bolus or as an extended bolus (square bolus) over a certain period of time, which allows a better match between insulin delivery and glucose absorption from the meal in patients with abnormalities of gastric emptying. Use of an insulin pump should be considered in the following patients:

- Patients unable to achieve target goals with basal-bolus regimens
- Patients with frequent hypoglycemia, dawn phenomenon, or brittle diabetes
- Pregnant patients
- Patients with insulin sensitivity or those requiring more intense monitoring due to complications.

Recently, continuous glucose monitors have been developed that measure interstitial glucose levels. Continuous glucose monitoring has been shown to lower HbA1c in adult patients with type 1 DM.²⁹

Gestational diabetes

In patients with gestational diabetes, insulin therapy is indicated when exercise and nutritional therapy are ineffective in controlling prandial and fasting blood glucose levels. Basal therapy alone may be sufficient, but a basal-bolus regimen is often required.⁸

Summary

- Glycemic control reduces the development and progression of complications of diabetes such as retinopathy, nephropathy, and neuropathy.
- The primary techniques available to assess the quality of a patient's glycemic control are self-monitoring of blood

glucose and interval measurement of HbA1c.

- Available treatment options to control blood glucose include insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, incretin-based therapies, SGLT-2 inhibitors, amylinomimetics (pramlintide), dopamine-receptor agonist (bromocriptine), and insulin.

References

- Mitka M. Report quantifies diabetes complications. *JAMA* 2007; 297:2337–2338.
- Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 2005; 28:1510–1517.
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published erratum appears in *Lancet* 1998; 352:1558]. *Lancet* 1998; 352:854–865.
- Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA* 1989; 261:1155–1160.
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329:977–986.
- Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD. Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. *BMJ* 1999; 319:83–86.
- Bergenstal RM, James GR III; Global Consensus Conference on Glucose Monitoring Panel. The role of self-monitoring of blood glucose in the care of people with diabetes: report of a global consensus conference. *Am J Med* 2005; 118(suppl 9A):15–6S.
- American Diabetes Association. Standards of medical care in diabetes—2017: summary of revisions. *Diabetes Care* 2017; 40(suppl 1):S1–S135.
- Schwedes U, Siebolds M, Mertes G; for the SMBG Study Group. Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. *Diabetes Care* 2002; 25:1928–1932.
- Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. *JAMA* 2006; 295:1688–1697.
- Delamater A. Clinical use of hemoglobin A1c to improve diabetes management. *Clinical Diabetes* 2006; 24:6–8.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; 38:140–149.
- Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193–203.
- Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; 334:574–579.
- Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992; 15:755–772.
- Dormandy JA, Charbonnel C, Eckland DJ, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366:1279–1289.
- Fonseca VA, Kulkarni KD. Management of type 2 diabetes: oral agents, insulin, and injectables. *J Am Diet Assoc* 2008; 108(4 suppl 1):S29–S33.
- Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy—update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2008; 31:173–175.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [erratum published in *Lancet* 1999; 354:602]. *Lancet* 1998; 352:837–853.
- Chiaasson J-L, Josse RG, Gomis R, Hanefeld M, Karsik A, Laakso M; for the STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM Trial. *JAMA* 2003; 290:486–494.
- Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk; 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf. Accessed June 26, 2017.
- Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies viewpoints on the way to consensus. *Diabetes Care* 2009; 32(suppl 2):S223–S231.
- Zinman B, Wanner C, Larchin JM; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373:2117–2128.
- Abdul-Ghani MA, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev* 2011; 32:515–531.
- Symlin (Pramlintide acetate) [package insert]. Wilmington DE: Astra-Zeneca; 2015. Pharmaceuticals LP. http://www.azpicentral.com/symlin/pi_symlin.pdf#page=1. Accessed June 26, 2017.
- Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010; 33:1503–1508.
- Cycloset [package insert]. Tiverton, RI: VeroScience LLC; 2016. <http://www.veroscience.com/documents/CyclosetPackageInsertFeb062017.pdf>. Accessed June 26, 2017.
- Hirsch IB, Bergenstal RM, Parkin CG, Wright Jr, E, Buse JB. A real-world approach to insulin therapy in primary care practice. *Clinical Diabetes* 2005; 23:78–86.
- Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; 359:1464–1476.

Correspondence: Mario Skugor, MD, Endocrinology and Metabolism Institute, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; skugorm@ccf.org