Treatment of Type 2 Diabetes and the Role of Insulin

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Treatment of Type 2 Diabetes and the Role of Insulin

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Introduction

In 2005, the Centers for Disease Control and Prevention (CDC) estimated that 20.8 million people in the United States had diabetes, 6.2 million of whom were undiagnosed.[1] Approximately 8.7 percent of non-Hispanic whites in the United States have diabetes. The estimated prevalence is considerably higher among other ethnic groups: 13.3 percent for non-Hispanic blacks, 9.5 percent for Hispanics/Latino Americans, and 15.1 percent for American Indians and Alaska Natives.[1] These numbers are expected to increase dramatically in the first half of the century.[1,2]

Type 2 diabetes, which accounts for almost 95 percent of all diagnosed cases of diabetes, is still primarily a disease of adulthood, although clinical and regional reports suggest that it is being diagnosed more frequently among children and adolescents.[1] The increasing prevalence of the disease makes its prevention, when possible, and its management, key medical priorities for primary care physicians, who provide care to more than 75 percent of patients in the United States who have type 2 diabetes.[3] Family physicians have the opportunity to guide patients on the path to successful diabetes management, resulting in optimal health and an improved quality of life.

Risk Factors, Complications and Disease Burden

Older age, obesity (particularly intra-abdominal adiposity), physical inactivity, family history of diabetes and ethnicity are risk factors for type 2 diabetes.[1,4] To date, no single causative factor has been identified for type 2 diabetes.[4,5]

On the basis of data from 2002, the CDC estimated that the mortality risk among people who have diabetes is approximately twice that of age-matched people who do not have the disease.[1] Further, adults who have diabetes are two to four times more likely to die of heart disease or have

Learning Objectives

After reading this monograph, you should be able to:

1. Explain the burden of disease for poorly controlled type 2 diabetes in terms of cost, cardiovascular complications and overall health outcomes.
2. Describe the evidence-based rationale for prescribing insulin for patients who have type 2 diabetes that is not adequately controlled with lifestyle changes and oral medication.

a stroke. Heart disease and stroke are responsible for approximately 65 percent of deaths among patients who have diabetes; hypertension affects almost 75 percent of adults who have diabetes. Microvascular complications of diabetes are also common. Among adults, diabetes is the most frequent cause of new cases of blindness and the leading cause of kidney failure, accounting for almost half of all new cases. More than 60 percent of all nontraumatic lower-limb amputations are performed on patients who have diabetes. Poorly controlled diabetes can also cause birth defects, miscarriages, diabetic ketoacidosis, periodontal disease, and higher susceptibility to, and risk of death from, illnesses such as pneumonia and influenza.[1] The direct and indirect financial costs of diabetes are also considerable; in 2002, the total cost of diabetes in the United States was estimated to be $132 billion.[6] The cost in terms of patients' quality of life cannot be calculated.

Prevention

Early identification and management of risk factors can prevent or delay the onset of diabetes. Estimates indicate that at least 54 million adults in the United States have prediabetes, defined as the presence of impaired fasting glucose (IFG) (fasting blood glucose levels of 100 mg per dL to 125 mg per dL after an overnight fast), impaired glucose tolerance (IGT) (blood glucose levels of 140 mg per dL to 199 mg per dL after a 2-hour oral glucose tolerance test) or both.[1]

Metabolic syndrome, which predisposes individuals to diabetes, is defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) as the presence of three or more of the following characteristics[7]:

- Waist circumference greater than 102 cm (40 in) in men and greater than 88 cm (35 in) in women
- Triglyceride levels greater than or equal to 150 mg per dL
- High-density lipoprotein (HDL) cholesterol levels less than 40 mg per dL in men and less than 50 mg per dL in women
- Blood pressure greater than or equal to 130/85 mm Hg
- Fasting glucose greater than or equal to 110 mg per dL

According to data from the Third National Health and Nutrition Examination Survey (NHANES III), almost 25 percent of adults in the United States meet the criteria for metabolic syndrome.[8] The highest age-adjusted prevalence is among Mexican Americans, and the overall prevalence increases with age.

Just as they are the cornerstone of treatment for diagnosed type 2 diabetes, lifestyle modifications, including appropriate nutrition, sufficient physical activity and smoking cessation, help reduce the risk of diabetes. In several studies, diet and exercise were shown to reduce the incidence of type 2 diabetes by more than 50 percent among people who had IGT, thus also reducing cardiovascular risks.[9-11] The importance of diet in preventing type 2 diabetes is highlighted by changes observed in indigenous populations. For example, the results of one study of Pima Indians living in the United States suggested that adopting a Westernized diet may have increased their risk of developing diabetes.[12] Consuming a traditional diet that included grains, squash, legumes and melons was associated with a lower risk of diabetes. In an Australian study, a group of middle-aged overweight and obese Aboriginal people ate a diet similar to that of their hunter-gatherer forebears for seven weeks; they lost weight and experienced improvement in the metabolic abnormalities associated with diabetes.[13]

Certain drugs used to treat type 2 diabetes also have potential for preventing the disease. In a study by the Diabetes Prevention Program Research Group, metformin

(Fortamet, Glucophage, Glumetza, Riomet) treatment reduced the incidence of diabetes by 31 percent compared with placebo.[14] By comparison, intensive lifestyle modification reduced the incidence of diabetes by 58 percent compared with placebo; the advantage of intensive lifestyle modification over metformin was greater among study participants who had a lower body mass index (BMI) and older patients than among study participants who had a high BMI and younger patients. Acarbose (Precose) reduced the absolute risk of progression from IGT to diabetes by 9 percent compared with placebo in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM); this effect was consistent among all age groups and BMI values.[15] Another trial showed that rosiglitazone (Avandia), when combined with lifestyle recommendations, substantially reduced the risk of diabetes in people who had IFG and/or IGT[16]; however, the potential risk for cardiovascular events associated with this drug may preclude its use in diabetes prevention.

Principles of Management

Best practices in family medicine include an aggressive approach to diabetes education upon diagnosis and on an ongoing basis. The patient should make an initial visit to a nutritionist and a diabetes educator who can teach the essentials of self-management, with additional visits as needed if the patient is not meeting treatment goals. Therapies for hyperglycemia prevention, blood pressure control and lipid management should also be pursued aggressively in order to prevent long-term complications. Most patients who have diabetes are best served by a multidisciplinary team that is individualized to their complex needs. In addition to a nutritionist and diabetes educator, members of this multidisciplinary team typically include an ophthalmologist and other specialists as needed if the patient develops cardiovascular, renal, neurological or podiatric complications. Referral to an endocrinologist should be considered early on in the care of patients who have type 2 diabetes and are not able to meet treatment goals despite attempts at aggressive therapy. Family physicians who have less experience in the management of type 2 diabetes may wish to refer patients to an endocrinologist for help with the development of an optimal treatment plan either at the time of diagnosis or when insulin therapy is initiated.

It is generally accepted that good glycemic control reduces the risk of certain diabetes-related complications.[9] The American Diabetes Association (ADA) defines blood glucose control as a general target A1C of less than 7 percent, whereas the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) have proposed a target A1C of less than 6.5 percent.[10,17,18] The ADA also recommends that goals should be individualized for patients on the basis of their particular circumstances, noting that more stringent goals (e.g., a normal A1C goal of less than 6 percent for selected patients) might reduce the risk of complications but also might increase the risk of hypoglycemia.[17,19] The American Academy of Family Physicians (AAFP) also emphasizes the need to consider individual patients' preferences and risk profiles when setting glycemic goals and states that the benefits of glycemic control should be weighed against the potential risks involved in achieving that control.[20]

In 2006, the ADA and the European Association for the Study of Diabetes co-developed by consensus an algorithm for the management of hyperglycemia in type 2 diabetes *(Figure 1).* In 2007, the AACE and the American College of Endocrinology collaborated to formulate the three evidence-based "Road Maps" for achieving glycemic control in type 2 diabetes (accessible

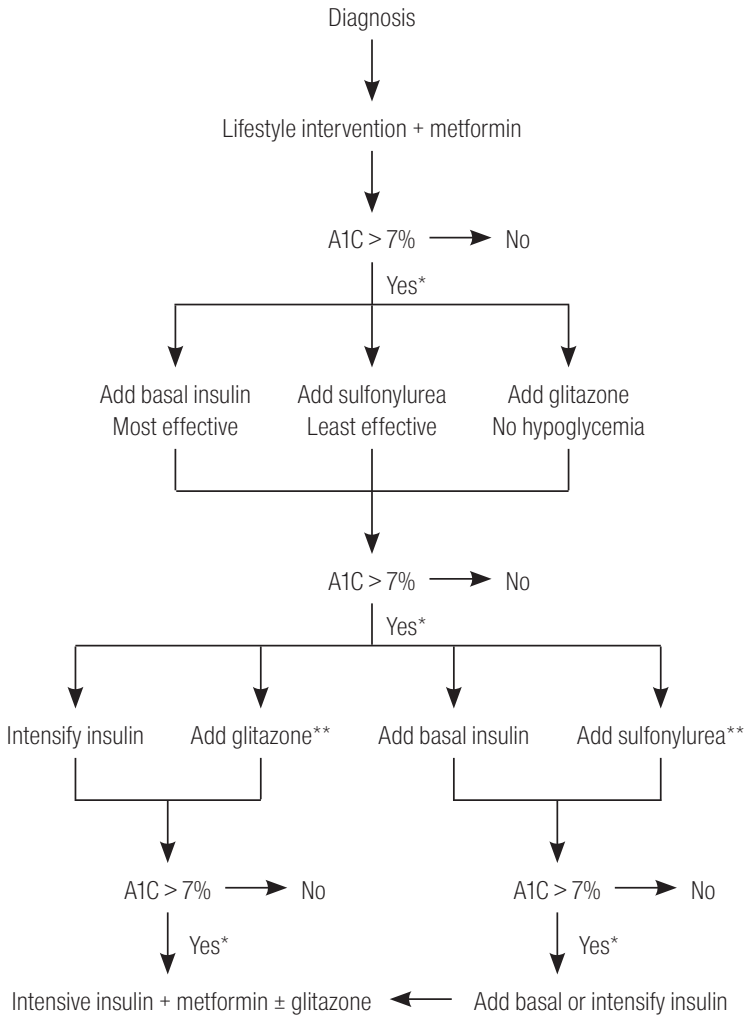
online at http://www.aace.com/meetings/consensus/odimplementation/roadmap.pdf). The first is for treatment-naïve patients; the second applies to patients undergoing treatment who have not achieved their target A1C levels. The third addresses diabetes prevention. Both groups emphasize lifestyle modification as the first and most constant component of any treatment strategy, and identify metformin as the preferred first-line pharmacologic therapy for most patients. Both groups also advise that insulin therapy be considered early in the course of type 2 diabetes.[21,22]

Pharmacologic Treatment Options

Although appropriate diet, regular physical activity and smoking cessation are the first-line interventions for type 2 diabetes, most patients eventually need some form of pharmacotherapy. This need typically evolves over time into a need for multiple medications.[21] A number of drugs with various mechanisms of action are available for use as monotherapy or in combination *(see Table 1).*

Insulin sensitizers include the biguanide metformin and the thiazolidinediones pioglitazone (Actos) and rosiglitazone. Metformin increases hepatic insulin sensitivity and also may slightly increase muscle insulin sensitivity. Because it is relatively inexpensive, is generally well tolerated, does not lead to weight gain and has a favorable safety profile, metformin is considered the first-line oral agent for type 2 diabetes. However, it should not be used in patients who have compromised renal or hepatic function, or significant cardiac disease. The thiazolidinediones increase skeletal muscle, hepatic and adipose tissue sensitivity to insulin, but

Figure 1. Algorithm for the Metabolic Management of Type 2 Diabetes



* Check A1C every 3 months until < 7% and then at least every 6 months.
** Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

may cause hepatic failure and should not be used in patients who have hepatic or cardiac disease.

In November 2007, the U.S. Food and Drug Administration (FDA) added information to the black box warning for rosiglitazone. The revised warning includes the following statement: "A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive." [23] No conclusive evidence is available regarding whether or not this is a class effect. A meta-analysis of pioglitazone trials suggested lower risk of death, myocardial infarction or stroke among a broad population of patients who had diabetes; the incidence of serious heart failure was increased, without an associated increase in mortality.[24] Physicians have been advised to individualize treatment with thiazolidinediones carefully, keeping these concerns in mind.[25,26]

Insulin secretagogues, which stimulate pancreatic insulin secretion, include the long-acting sulfonylureas (glipizide [Glucotrol], glyburide [Diabeta, Glynase, Micronase] and glimepiride [Amaryl]) and the short-acting meglitinides (repaglinide [Prandin]) and D-phenylanalanine derivatives (nateglinide [Starlix]). All insulin secretagogues can cause hypoglycemia, although the meglitinides' shorter duration of action makes this less likely to occur.[26] Because

Table 1. Noninsulin Medications for Type 2 Diabetes

Type	Class	Examples	Primary Action
Insulin sensitizers	Biguanide	Metformin (Fortamet, Glumetza, Glucophage, Riomet)	Decrease hepatic glucose production, increase hepatic insulin sensitivity
	Thiazolidinediones	Pioglitazone (Actos), Rosiglitazone (Avandia)	Enhance insulin action, decrease hepatic glucose production
Insulin secretagogues	Sulfonylureas	Glipizide (Glucotrol), glyburide (Diabeta, Glynase, Micronase), glimepiride (Amaryl)	Stimulate β-cell insulin release
	Meglitinides	Repaglinide (Prandin), nateglinide (Starlix)	Stimulate β-cell insulin release
Other oral drugs	DPP-4 inhibitor	Sitagliptin (Januvia)	Prevent GLP-1 breakdown, reducing blood glucose levels
	α-glucosidase inhibitors	Acarbose (Precose), miglitol (Glyset)	Block starch breakdown, slow breakdown of some sugars
Injectables	GLP-1 mimetic	Exenatide (Byetta)	Stimulate insulin secretion, suppress glucagon secretion, promote β-cell production
	Amylin analog	Pramlintide (Symlin)	Act with insulin to delay gastric emptying, inhibit glucagon release

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide.

Information from A, B and C.

they are effective, relatively inexpensive and generally well tolerated, sulfonylureas are usually considered to be the first choice in this drug class. However, they may cause weight gain in some patients.

Alpha-glucosidase inhibitors (acarbose and miglitol [Glyset]) slow the body's absorption of carbohydrates, thus lowering postprandial glucose levels with no risk of hypoglycemia. The increase in carbohydrates delivered to the colon can cause gas and other distressing gastrointestinal symptoms that may make adherence difficult.[21,25] The dipeptidyl peptidase-4 inhibitor sitagliptin (Januvia) prolongs the activity of proteins that boost postprandial insulin release, resulting in improved glucose control, particularly postprandial.[25]

Exenatide (Byetta) and pramlintide (Symlin) are two relatively new injectable drugs. Exenatide is an incretin (glucagon-like peptide-1) mimetic and pramlintide is a synthetic analog of amylin, which is secreted by β-cells in response to increased glucose levels. Pramlintide is used with mealtime insulin and is indicated for patients who have type 1 diabetes and for patients who have type 2 diabetes whose glucose levels are not adequately controlled by optimal therapy with insulin or insulin with metformin or a sulfonylurea. Exenatide is indicated in patients who have type 2 diabetes when treatment with metformin, a thiazolidinedione, a sulfonylurea or a combination of those drugs does not achieve adequate glycemic control. It has not been studied in conjunction with insulin and it is not indicated for patients who have type 1 diabetes or for those who have type 2 diabetes who take insulin. Exenatide and pramlintide both have favorable effects on body weight and A1C, but both also have potential adverse effects, including hypoglycemia.[27]

Other important therapeutic considerations include angiotensin-converting enzyme (ACE) inhibitors (or, alternatively, angiotensin receptor blockers [ARBs]) for treatment of hypertension or microalbuminuria, statin therapy for dyslipidemia, pneumococcal and influenza vaccines, yearly ophthalmology referrals and close monitoring for other complications.

Insulin

Among younger people who have type 2 diabetes, tight glycemic control is an essential component in reducing the risk for complications. Although insulin is often reserved as a treatment of last resort,[28] when glucose levels are not adequately controlled with lifestyle modifications and other diabetes medications, initiation of insulin is preferred over extended treatment with oral agents. In patients who have extremely high glucose levels or significant symptoms, the physician may consider initiating insulin immediately, though not necessarily permanently. In general, the goals of insulin therapy are to reach the patient's target A1C level while avoiding hypoglycemic episodes and weight gain[3]; as always, the treatment regimen should be individualized for each patient. When starting insulin therapy, the complexity of the regimen, the possibility for weight gain, patient fears and concerns, and management of comorbid conditions should be taken into consideration.

Most patients' β-cell function declines over time despite treatment.[3] When a patient does not achieve his or her A1C goal with lifestyle measures, oral therapy or the addition of exenatide injections, insulin usually becomes necessary. Adding basal insulin to oral treatment offers the potential advantages of a lower starting insulin dose and an initial insulin regimen consisting of only one bedtime injection.[29] Combining basal insulin with oral medications is more effective for achieving A1C goals than insulin monotherapy. If this combination does not control postprandial glucose levels and more insulin is needed, a prandial insulin can be added.[30]

Table 2 summarizes the timing of the action of various types of insulin. Long-acting basal insulins currently on the market include glargine (Lantus), detemir (Levemir) and neutral protamine Hagedorn (NPH) (Humulin N, Novolin N). These long-acting insulins are intended to replace the normal fasting insulin secretion of pancreatic β-cells. The introduction of insulin glargine provided the first insulin analog with a relatively peakless 24-hour glucose-lowering profile,[31,32] although glargine's effects may not always last 24 hours and can still require two injections a day. Detemir's duration of action is somewhat shorter than that of glargine; although it can be dosed once to twice daily, most patients may need to use it twice a day to achieve glycemic control.[26] Limited research suggests that detemir provides glycemic control similar to NPH insulin; however, patients who have type 2 diabetes who use detemir may be slightly less likely to experience weight gain.[33] Potential benefits must be weighed against its cost. NPH remains the least expensive long-acting insulin, though its duration of action usually requires twice daily injections. Regular insulin is as effective as the short-acting insulin analogues and can be considerably less expensive. For patients who can manage the timing and frequency of multiple daily injections, and for those who cannot afford the alternatives, regular insulin is a reasonable option. However, some patients find the challenge of coordinating meal times with injections to be overwhelming, and in these cases, the short-acting insulins are more practical.

Rapid-acting insulin analogs (aspart [Novolog], lispro [Humalog], and glulisine [Apidra]) have a quick onset of action and a shorter half-life than regular insulin, and are used to replace the increased insulin secretion that typically follows food intake. These insulins can be injected at mealtime (from immediately before eating until immediately after) and their more rapid dissipation closely mimics digestion, eliminating the need for between-meal snacks. The combined use of a consistent basal insulin with mealtime insulin to control glucose excursions closely mimics normal, or physiologic, insulin secretion by β-cells *(Figure 2).*[3]

Temporary insulin use has also been proposed for patients who are symptomatic, have infections at the time of diagnosis,

Table 2. Timing of Insulin Activity

Type	Onset (h)	Peak (h)	Duration of Effect (h)	Recommended Interval Between Dosing and Meal Initiation (min)
Aspart (Novolog)	0.25	1 to 3	3 to 5	10 to 20
Lispro (Humalog)	0.25	0.5 to 1.5	2 to 5	15 (or immediately after a meal)
Glulisine (Apidra)	<0.25	0.5 to 1.5	1 to 2.5	15 (or within 20 minutes after starting a meal)
Regular (Humulin R, Novolin R, Velosulin BR)	0.5 to 1	2 to 4	8 to 12	30 to 60
NPH (Humulin N, Novolin N)	1 to 1.5	4 to 12	24	
Glargine (Lantus)	1 to 2	None*	Up to 24*	
Detemir (Levemir)	6 to 8	3 to 14	5 to 24	

NPH = neutral protamine Hagedorn; h = hours; min = minutes.

*—According to the authors, although the introduction of insulin glargine provided the first insulin analog with a relatively peakless 24-hour glucose-lowering profile, insulin glargine's effects may not always last 24 hours and can still require two injections a day.

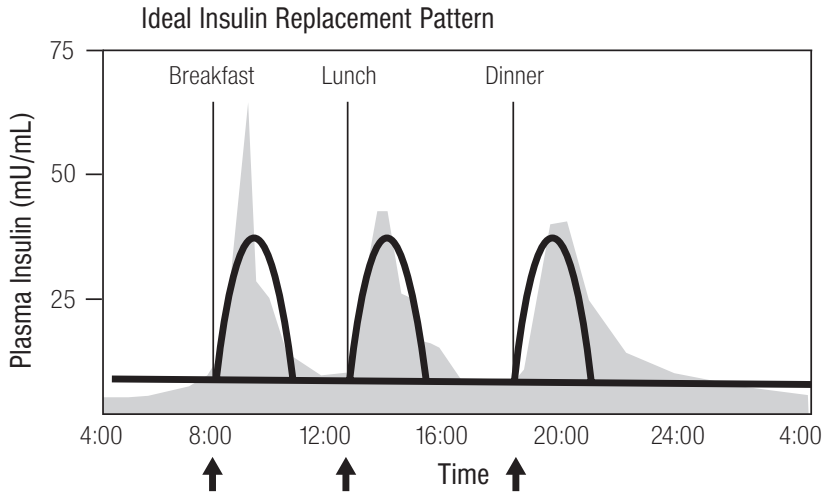
Information from references C and D.

are on corticosteroid therapy or have very high glucose levels. For example, use of aggressive short-term insulin therapy has also been investigated for rapidly achieving glycemic control in people who are newly diagnosed with type 2 diabetes and who have severe hyperglycemia.[34] Hospitalized patients whose blood glucose is not well controlled can be managed with an insulin infusion. Healing after surgery or recovering from an infection is aided by optimal glucose control, and an insulin regimen can be continued outside the hospital setting until full recovery. Although oral medications are being used more frequently during pregnancy, insulin is still utilized most often to ensure tight glycemic control.

Several insulin delivery systems are currently available for patients taking insulin, and each has its advantages and disadvantages *(Table 3).* Insulin pens, which contain premeasured doses of insulin, may be appropriate for patients who fear needles. One study showed that medication adherence rates among patients who switched from an oral agent to an insulin pen were comparable to adherence rates among patients who switched from an oral agent to an insulin syringe.[35] Although the pens are initially more expensive than syringes, there is no waste of insulin; pens may end up being more cost-effective than syringes through reduced health care resource utilization and associated costs.[35] They may also be useful for patients who have difficulty loading syringes due to limited dexterity or vision problems. Insulin pumps may be an attractive alternative for patients who experience difficulty achieving tight glycemic control while avoiding hypoglycemia. Insulin pumps are useful in treating type 1 diabetes and may be used in motivated patients who have type 2 diabetes; however, these pumps are currently quite expensive. Inhaled insulin was recently taken off the market by the manufacturer owing to lower-than-expected sales. Other companies are researching the development of inhaled insulin products.

Some patients may be reluctant to use insulin. This reluctance may stem from the idea that needing insulin denotes failure on

Figure 2. Basal-bolus Insulin Therapy to Mimic Normal Secretion



The shaded area represents a normal insulin-release pattern.

Reprinted with permission from Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue augmentation, and replacement of beta-cell function. Am Fam Physician 2004;70:489-500,511-512.

their part or from concern that using insulin will negatively impact their lifestyle.[29] Patients may also have a fear of needles or the pain of an injection, or worry about hypoglycemia or weight gain. To address patient reluctance, education and encouragement are necessary. Avoid using the prospect of insulin as a threat to motivate adherence to lifestyle changes (e.g., "If you don't exercise, I'll have to put you on insulin."). Also, demonstrate to the patient that insulin injections are typically less painful than finger sticks for blood glucose monitoring, and explain that, with several insulin delivery options, pain and lifestyle disruption can be minimal.[29]

Self-management

Self-management is a necessary component of a diabetes treatment plan, since the responsibility for daily care and monitoring usually falls to the patient. Patient education ensures that the patient is aware of the complications that can arise from uncontrolled diabetes and the means for achieving control. Although a diabetes educator trained specifically for this task may be an ideal source of information for patients (to find a diabetes educator in your area, visit the American Association of Diabetes Educators [AADE] Web site at http://www.diabeteseducator.org/DiabetesEducation/Find.html), family physicians, nurses and endocrinologists can, and do, provide much education on these topics.

Frequency of self-monitoring of blood glucose in a patient who has type 2 diabetes should be tailored according to the type of treatment being used and whether the patient has achieved his or her glycemic goal. Certain situations, such as an acute illness or a period of medication adjustment, call for increased frequency of monitoring.

In most cases, patients who use multiple daily injections of insulin, either as monotherapy or combined with oral antidiabetic agents, to treat type 2 diabetes should monitor their blood glucose as often as patients who have type 1 diabetes do (i.e., three or more times per day).[36] However, some patients may not need to test as frequently (e.g., a patient who is using insulin for basal supplementation). The peak action period of the insulin(s) used by the patient, as well as the timing of meals and physical activity, should determine specific daily testing times. When a patient's insulin dosage(s) need to be adjusted, postprandial sugar levels are as important as fasting levels, as adjustments to the basal insulin are based on the fasting glucose level and adjustments to rapid-acting insulin are based on the postprandial readings.

The value of self-monitoring for patients who have type 2 diabetes and are not using insulin is controversial. A large managed care study found that a reduction in the frequency of self-monitoring resulted in cost savings (calculated on the basis of a reduction in testing strip use) with no significant impact on

Table 3. Insulin-Delivery Systems

Type	Advantages	Disadvantages
Syringe	Maximal dosing flexibility	Cumbersome to carry Can be difficult to distinguish insulin types
Pen	Less cumbersome Easy to distinguish between insulin types by pen color/size More accurate dosing No waste Preferred by patients over syringe	Potentially more expensive
Pump	Fewer injections Physiologic delivery with best glycemic control and fewest hypoglycemic events overall	Expensive Requires training Not suitable for most nonsevere type 2 diabetes Potential for technical problems

Information from references E and F.

individual glycemic control in a group of patients who had relatively stable type 2 diabetes and did not use insulin.[37] Patients have reported an overall impression that the results of their self-monitoring are of no significance to physicians and sometimes discontinued testing as they became more familiar with the physical signs of hypoglycemia.[38] For asymptomatic patients who achieve stable glycemic control using oral medications alone, being tested every three months by a physician may be adequate.

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