Progressive hyperglycemia is a characteristic of type 2 diabetes mellitus (T2DM) that poses a challenge to maintaining optimal glycemic control. Achieving glycemic control early in the course of disease can minimize or prevent serious complications. Most patients with T2DM eventually require insulin replacement therapy to attain and preserve satisfactory glucose control. For decades, the use of insulin to address the primary defect of T2DM has been a cornerstone of diabetes therapy. Insulin is indicated for patients with T2DM presenting with clinically significant hyperglycemia, and it is mandatory for patients exhibiting signs of catabolism. Insulin should be considered for patients in whom hyperglycemia persists despite attempts to control the condition through diet and exercise modifications and the use of noninsulin therapies. Many physicians delay initiation of insulin until absolutely necessary, sometimes overestimating patient concerns about its use. Modern insulin analogs, treatment regimens, and delivery devices make insulin more user friendly, and physicians can promote patient acceptance of insulin by reviewing the benefits of controlled glycated hemoglobin levels and addressing patient concerns.

Pathophysiologic Profile: Increasing Insulin Deficiency

Type 2 diabetes mellitus is a disease of dysfunctional glucose metabolism that is characterized by worsening hyperglycemia and a loss of response to therapy over time. Insulin resistance is an early factor in the pathophysiologic profile of T2DM, which may be associated with unhealthy lifestyle choices and weight gain. However, weight loss will not ameliorate all problems associated with T2DM. Insulin release declines progressively in patients with T2DM and begins well before diagnosis. In fact, studies suggest that 50% to 80% of β-cell function is lost by the time of diagnosis. The decline continues as the disease progresses, from impaired fasting glucose levels and impaired glucose tolerance to full-blown T2DM, and it continues to progress until the patient becomes increasingly insulin deficient. Figure 3 depicts the changes in insulin resistance and insulin secretion that occur over time in patients with T2DM. A decline in β-cell function leads to persistent hyperglycemia.

In many patients, the metabolic abnormalities associated with persistent hyperglycemia lead to complications such as vision loss, renal failure, and neuropathy. Moreover, T2DM is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States, and it is a major cause of heart disease and stroke. It is imperative that increased measures are taken to improve rates of glycemic control in patients with T2DM. In addition, appropriate intervention can often forestall the development of microvascular complications in many patients. The earlier that patients can establish glycemic control, the better.
Treatmen Goals

The goal of T2DM therapy is to reestablish normoglycemia and avoid both the excesses of hyperglycemia and the dangers associated with hypoglycemia. For patients with T2DM, the goals for a patient-centered approach to glycemic treatment are evidence based and are predicated on data from landmark trials showing reductions in the microvascular complications of diabetes mellitus associated with glycated hemoglobin (HbA1c) levels of less than 7%; these levels generally correspond to premeal or fasting glucose levels of 70 mg/dL to 130 mg/dL and postprandial glucose levels of less than 180 mg/dL. In the past 2 years, however, most major organizations have recognized the need for an individualized approach to both treatment goals and treatment options, weighing both the risks and the benefits to the patient. In 2012, the American Diabetes Association (ADA), in conjunction with the European Association for the Study of Diabetes (EASD), issued a position statement for the management of hyperglycemia that emphasizes a patient-centered approach, with the avoidance of hypoglycemia considered a primary tenet, particularly in at-risk patients. The ADA and the EASD suggest less stringent goals for HbA1c levels (7.5% to 8.0%) for patients with a history of severe hypoglycemia, a limited life expectancy, advanced complications, or extensive comorbid conditions, or for those who have difficulty attaining glycemic control, drawing on lessons from studies by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Veterans Affairs Diabetes Trial (VADT), and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. However, for younger patients or for patients with disease of short duration, a long life expectancy, and no significant cardiovascular disease, HbA1c goals closer to normal (eg, 6.0% to 6.5%) are recommended. The American Association of Clinical Endocrinologists concurs with the individualization of treatment goals and has led the way to the development of a comprehensive care plan for patients with T2DM. Paying attention to cardiovascular risk factors (eg, high blood pressure, high cholesterol levels) is important for all patients with T2DM, as is focusing on glucose control.

Current Treatment Recommendations

The position statement of the ADA and the EASD quotes the Committee on Quality of Health Care in America of the Institute of Medicine in defining patient-centered care as an approach “to providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.” This position statement acknowledges that glycemic management in patients with T2DM has become increasingly complex and, to some extent, controversial, considering the increasing number and type of pharmacologic agents now available. I truly believe in a patient-centered approach. The patient has to be part of the decision-making process. I talk to all of my new patients, and I explain every different medication that is available. I tell them about the risks and benefits of the medications, and I let them decide which medication to take.

Management of T2DM consists of interventions designed to affect the physical activity levels and food intake of an individual. However, current treatment...
recommendations now also include initiation of pharmacotherapy at the time of diagnosis, in part as a result of our improved understanding of the pathophysiologic profile of T2DM.12,18

Metformin, which has been used for decades in the management of T2DM, continues to be considered a cornerstone of therapy, and it remains the most widely used first-line therapy for this disease.19 Its mechanism of action predominantly involves reducing hepatic glucose production. Metformin is generally considered weight neutral, and it is not associated with hypoglycemia.

Metformin therapy has been shown to reduce the risk of microvascular complications associated with T2DM. The United Kingdom Prospective Diabetes Study9 demonstrated a reduction in the rate of mortality from all causes in a subgroup of obese patients with T2DM treated with metformin; this finding was also confirmed in a 10-year postinterventional follow-up study.10 Decision making is based on the needs and characteristics of individual patients, including their comorbidities, their hyperglycemia levels, and numerous other factors.18 Ultimately, patients make the final decisions regarding their lifestyle choices and, to some extent, the pharmaceutical interventions that they use. Certainly, adoption of and adherence to therapy occur in the context of the real lives of the patients. Patient involvement in medical decision making constitutes one of the core principles of an osteopathic physician’s clinical practice.

Figure 2.
Proportion of 18-year-olds in the United States who will develop diabetes, by sex, body mass index (BMI), and period, as determined by the American Diabetes Association. Reprinted with permission from the American Diabetes Association, from Cunningham SA, et al. Decreases in diabetes-free life expectancy in the U.S. and the role of obesity. *Diabetes Care*. 2011;34(10):2225-2230; permission conveyed through Copyright Clearance Center, Inc.

Figure 3.
Insulin Therapy

Insulin, like metformin, is a cornerstone of T2DM therapy. By activating the insulin receptor, exogenous insulin therapy increases peripheral glucose uptake and suppresses hepatic glucose production. Outcome studies have also provided evidence that insulin therapy reduces the risk of microvascular complications associated with T2DM. More than 90 years of clinical experience with insulin support its use. Insulin is universally effective in lowering glucose and HbA1c levels. Any insulin dose will lower these levels in a dose-related manner, and the upper threshold of the dose is limited only by the associated risk of hypoglycemia. Although many physicians delay using insulin therapy until the development of later stages of disease or extremely high levels of hyperglycemia, insulin therapy can be initiated at any HbA1c level in patients with T2DM. Insulin therapy is simply one of the many effective therapeutic options for which assessment of the risk-benefit ratio of a patient’s particular medical history is warranted. Specific indications for insulin therapy are discussed in the following paragraphs and are summarized in Table 1.

Initiation of insulin therapy is indicated for patients with T2DM who present with clinically significant hyperglycemia and is mandatory for those with signs of catabolism (eg, weight loss and ketosis). It is strongly recommended for patients with extreme hyperglycemia (ie, a blood glucose level ≥300-350 mg/dL or an HbA1c level ≥10%-12%). Oral noninsulin therapies decrease HbA1c levels by approximately 0.5% to 1.5%. Therefore, if patients have HbA1c levels of more than 9%, insulin may be the most appropriate treatment option, as suggested by the American Association of Clinical Endocrinologists. However, as discussed in reviews by Garber and Freeman, emerging data also indicate that some of the long-acting glucagon-like peptide-1 receptor agonists result in robust lowering of the glycemic level. Insulin therapy should also be considered for patients who have hyperglycemia despite making lifestyle modifications (diet and exercise) and taking maximal doses of noninsulin therapies during a 3- to 6-month period. This is called the “step-up” approach. Waiting a long time before adjusting therapies should be avoided.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial provided an opportunity to observe glycemic control in a real-world setting. For 4900 patients who were allocated to receive placebo in the nonintervention arm of the study, diabetes control was measured at baseline and then yearly for a median of 5 years. The median HbA1c level was 6.9% at baseline, and it increased by an average of 0.22% over the course of 5 years (P < .001). Only 2% of patients at baseline and 4% of patients after 5 years were taking oral agents other than metformin or sulfonylureas. During a 5-year period, the percentage of patients using insulin increased to 32% (21% were also taking oral agents). Use of oral agents by patients remained similar (56% of patients during the same period). In 855 patients, initiation of insulin therapy produced a sustained reduction in the HbA1c level from a median of 8.2% to a median of 7.7%, with a weight gain of 4.6 kg occurring over the course of 5 years. In this trial, the need for insulin therapy doubled over 5 years.

Another philosophy involves starting intensive insulin therapy at the time of either initial patient presentation or diagnosis of T2DM. Evidence indicates that short-term use of intensive insulin therapy allows either more preservation or partial reversal of β-cell function in these patients, which allows them to have a normal glycemic profile and to continue with normal glycemia without diabetes medications for multiple

<table>
<thead>
<tr>
<th>Mandatory</th>
<th>Indicated</th>
<th>Consider</th>
<th>Supportive Data Exist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with catabolic features (weight loss, ketosis)</td>
<td>Patients with significant hyperglycemia</td>
<td>Other patients with hyperglycemia despite diet, exercise, and maximal doses of noninsulin therapies</td>
<td>First-line therapy in patients presenting with newly diagnosed type 2 diabetes mellitus</td>
</tr>
</tbody>
</table>
Attitudes and Initiation Concerns About Insulin Therapy

Many physicians prefer to delay initiation of insulin therapy until absolutely necessary. The reasons for this delay are partly attributed to the perceived concerns of patients, including the development of hypoglycemia and the pain associated with both injections and blood tests; however, data show that less than 20% of patients are truly unwilling to start insulin therapy (Figure 4). One of the most important messages to convey to patients is that they have not “failed” themselves or their physicians by needing insulin therapy. Patients need to understand that T2DM is a progressive illness. In the DAWN (Diabetes Awareness Wishes and Needs) survey, almost half of the patients believed that they were given insulin therapy because they had somehow “failed,” and they believed that the insulin therapy was their punishment. In patients with T2DM, a large percentage of β-cell function is already lost by the time of diagnosis, and it progressively declines; therefore, most patients with T2DM eventually will need insulin at some point in their lives. The need for insulin therapy does not mean that failure has occurred. Instead, the need for insulin is due to the progression of T2DM.

Delivery of the message regarding the value of insulin therapy, in addition to providing encouragement and education, can usually overcome any reticence on the part of patients. It is important to address the issues that may affect patient adherence, because the data do support a link between poor adherence and poor outcomes, including hospitalization and death. Patient initiation of and adherence to medication is influenced by many interrelated factors (Figure 5). Convenience and flexibility (ie, having therapy fit into the lifestyle of patients) are very important because they play into the ability of patients to adhere to therapy. Patients may skip insulin injections because the injections interfere with their lifestyle; therefore, fewer injections and the use of insulin pen delivery devices are preferred. Patients may also omit injections because they worry about hypoglycemia, which can be addressed in part by the use of insulin analogs and by patient education. Because insulin pen delivery devices allow patients the convenience of carrying their therapy with them, dosing accuracy is improved and administration is simplified. Insulin pump therapy might be an option for some patients who have erratic or spontaneous lifestyles and for patients for whom diet and exercise modifications are less predictable. Fewer injections are involved with the use of insulin pump therapy as well. Therapy can be adjusted to accommodate the vagaries of modern life. In summary, it is less likely that patients choose to be nonadherent and more likely that they struggle with the constraints that T2DM places on their lifestyle. By providing options that enhance the flexibility of therapy, we may be able to improve patient adherence and, ultimately, patient outcomes.

Patient education needs to take into account, among other things, patients’ years. (See also the article by Joseph Tibaldi, MD, in this supplement to The Journal of the American Osteopathic Association for further discussion of this topic.) The ADA supports this approach in their recommendations, stating the following: “In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA₁c, consider insulin therapy, with or without additional agents, from the outset.”
knowledge regarding insulin therapy, patients’ main concerns and perceived problem areas, collaborative goal setting and problem solving, and continued support. Some patients believe that insulin may cause harm. This belief dates back to times when insulin therapy was started so late in the disease process that its introduction coincided with the development of some of the very serious sequelae of T2DM, such as amputations resulting from diabetic neuropathy or blindness resulting from diabetic retinopathy. We need to be able to communicate to patients that insulin can help prevent the risks of these complications. Physicians can help patients accept insulin therapy by reviewing the benefits of HbA1c control and by addressing the myths and concerns about insulin therapy. We need to be sure that we are sending patients the right message about insulin therapy. Modern insulin analogs and treatment regimens make insulin a user-friendly therapy, as does the use of insulin pen delivery devices and even insulin pumps.

Table 2 provides some suggestions of how to respond to patient concerns about insulin therapy.27

Physiologic Insulin Replacement and Approaches to Starting Insulin

Ideally, the principle of insulin use is to create as normal a glycemic profile as possible without causing unacceptable weight gain or hypoglycemia. There are 2 specific insulin patterns: basal and prandial. The prandial pattern is further subdivided into first and second phases.

The light gray portions of Figure 6 show normal insulin release, which is what occurs in a healthy person. Figure 6 also shows how insulin analogs mimic that process fairly closely, with rapid-acting analogs providing prandial insulin coverage and with long-acting insulin analogs providing basal insulin needs. Figure 7 illustrates both human insulin profiles (regular and neutral protamine Hagedorn [NPH]) and in-

Figure 5.
Factors influencing medication initiation, adherence, and persistence.32
rather, is an intermediate-acting insulin) is compared with the long-acting insulin analogs (currently, insulin detemir and insulin glargine). Neutral protamine Hagedorn insulin has a peak, lasts on the order of 12 to 20 hours (rather than 24 hours), and often requires administration twice per day if it is used for basal coverage. The NPH insulin peak also increases the risk for hypoglycemia. A meta-analysis confirmed that basal insulin analog profiles. Rapid-acting insulins (insulin aspart, insulin glulisine, and insulin lispro) work fairly quickly, have a high peak, and return to baseline fairly quickly, a pattern that is similar to that of how food enters our system and leaves. This pattern is in contrast to how regular human insulin works. Regular human insulin takes longer to start working, so patients should administer it at least 30 minutes before eating to have the onset of action peak at the time that they need the insulin action. Human insulin also tends to last a little longer than needed, which may place the patient at a small risk of hypoglycemia. For these reasons, rapid-acting insulin analogs are considered to have a more physiologic profile than regular human insulin. These differences are more profound when NPH insulin (which is really not a basal insulin but, Table 2. Strategies to Address Patients' Concerns Regarding the Use of Insulin

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Strategies to Address Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense of loss of control</td>
<td>Counsel patients that they can take control of their diabetes by following an insulin regimen.</td>
</tr>
<tr>
<td>Belief that disease has worsened</td>
<td>Explain that most patients will require insulin because the body is not able to make enough insulin itself.</td>
</tr>
<tr>
<td></td>
<td>Show how insulin can be used to improve glycemic control at any point in therapy.</td>
</tr>
<tr>
<td>Sense of personal failure</td>
<td>Explain that insulin is required because of the natural course of diabetes, not patient behavior—it is inevitable and the patient could not have done anything to prevent it.</td>
</tr>
<tr>
<td></td>
<td>Introduce the possibility of insulin use at diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Do not use insulin as a threat for not dieting, exercising, or taking oral agents.</td>
</tr>
<tr>
<td>Injection-related anxiety</td>
<td>Show that needles are small and very fine.</td>
</tr>
<tr>
<td></td>
<td>Assure patient that injections are less painful than finger sticks for blood glucose self-monitoring.</td>
</tr>
<tr>
<td></td>
<td>Introduce prefilled insulin pens, which make injection very straightforward.</td>
</tr>
<tr>
<td>Perception that insulin is not effective</td>
<td>Explain that insulin improves glycemic control when used properly.</td>
</tr>
<tr>
<td></td>
<td>Assure patient that insulin will improve symptoms and make him or her feel better and have more energy.</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>Explain that some modern insulins have been shown to result in less weight gain than others.</td>
</tr>
<tr>
<td></td>
<td>Daily exercise can minimize weight gain and improve glycemic control.</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>Incidence of serious hypoglycemia is rare.</td>
</tr>
<tr>
<td></td>
<td>Modern insulin analogs are associated with less hypoglycemia, especially nocturnal hypoglycemia.</td>
</tr>
<tr>
<td></td>
<td>Teach about prevention, symptoms, and treatment of hypoglycemia.</td>
</tr>
<tr>
<td>Lack of confidence in ability to manage insulin therapy</td>
<td>Long-acting insulins are easily administered with the evening meal or at bedtime (detemir) or once daily at any time of day, but preferably at the same time of day (glargine).</td>
</tr>
<tr>
<td></td>
<td>Insulin pens make administration easier.</td>
</tr>
<tr>
<td></td>
<td>Diabetes educators are available.</td>
</tr>
<tr>
<td>Concerns of family, work, and friends</td>
<td>Explain that although taking insulin should not affect ability to work as long as treatment guidelines are observed, employers should be informed.</td>
</tr>
<tr>
<td></td>
<td>In general, patients should ensure that those close to them know everything they need to know.</td>
</tr>
</tbody>
</table>

Physicians need to balance the overall benefits and risks of therapies, but they also need to recognize that insulin replacement therapy addresses the primary defect. The overwhelming majority of patients with T2DM eventually require insulin therapy to achieve or preserve satisfactory glucose control and to achieve an HbA1c level of less than 7%. In general, the sooner insulin therapy is started, the better off patients will be in terms of avoiding complications.

**Patient Education and Self-Management**

It is important to help patients understand that insulin is not a last resort but is just another option, like the use of metformin, sulfonylureas, thiazolidinediones, and other secretagogues, as well as incretin therapies. However, multiple factors come into play when we consider using insulin to successfully treat patients with T2DM. The patient is the key factor in achieving treatment success. It is so important for patients to understand why they are taking insulin. Many times I have heard patients say, “The doctor just gave me this medication, and I was not really told why I should take it, so I just stopped taking it.” Patients need to understand why they are taking insulin, and they need to understand how to take it appropriately to decrease their risks for adverse effects and complications. Our job as physicians is to teach our patients. We need to help our patients choose the therapies that best fit their lifestyles and are cost effective, because otherwise they are not going to take their medications and receive their benefits. I often use an approach referred to as the “5C intervention.”

The basic premise of this intervention is to find out what is important to the patient on the day of their visit. An example is provided in Table 3.

**Conclusion**

Physicians need to balance the overall benefits and risks of therapies, but they also need to recognize that insulin replacement therapy addresses the primary defect. The overwhelming majority of patients with T2DM eventually require insulin therapy to achieve or preserve satisfactory glucose control and to achieve an HbA1c level of less than 7%. In general, the sooner insulin therapy is started, the better off patients will be in terms of avoiding complications.

References


### Table 3.
**Example of Patient Education and Self-Management of Type 2 Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Step</th>
<th>Goal</th>
<th>Conversation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constructing a problem definition</td>
<td>What is the patient’s concern or problem area?</td>
<td><strong>Patient:</strong> My HbA1c is starting to get high again—it’s 7.5%.</td>
</tr>
<tr>
<td>Collaborative goal setting</td>
<td>Set specific, measurable, action-oriented, and realistic goals</td>
<td><strong>Physician:</strong> I want your blood sugar levels in the morning between 70 and 130 mg/dL and I want your blood sugar levels after meals less than 180 mg/dL.</td>
</tr>
<tr>
<td>Collaborative problem solving</td>
<td>Identify barriers and formulate a strategy for success</td>
<td><strong>Patient:</strong> But when I go out and mow my grass, my blood sugar level drops, so I can’t take my insulin on the days I mow my grass.</td>
</tr>
<tr>
<td>Contracting for change</td>
<td>Track outcomes and reward successes</td>
<td><strong>Physician:</strong> On the days you mow your grass, take 2-3 units less of your prandial insulin before the meal around the time you mow the lawn. (If the patient just takes basal insulin, he or she should have a snack before mowing the lawn.)</td>
</tr>
<tr>
<td>Continuing support</td>
<td>Give positive reinforcement</td>
<td><strong>Physician:</strong> How did that work out? I’d like to review your blood sugar logs. You are getting good results—well done!</td>
</tr>
</tbody>
</table>


© 2013 American Osteopathic Association