CLINICAL THERAPEUTICS

Insulin-Pump Therapy for Type 1 Diabetes Mellitus

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

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N Engl J Med 2012;366:1616-24.

A 39-year-old man with type 1 diabetes of 27 years' duration visits his endocrinologist for review of his blood glucose control. He is overweight (body-mass index [the weight in kilograms divided by the square of the height in meters], 28.4). The overall glycemic control has been suboptimal, with glycated hemoglobin values of 7.5 to 8.0% in recent years. He reports unpredictable swings in self-monitored blood glucose concentrations and frequent episodes of severe hypoglycemia, which markedly disrupt his work and home life. He also reports that he now has fewer warning symptoms of hypoglycemia than he had previously. These findings are present despite the patient's best efforts to achieve glycemic control with intensified insulin-injection therapy, regular visits to a diabetes clinic, and input from diabetes nurse educators. He attended a structured diabetes education course 1 year previously, which he found to be useful and which led to slight improvements in glycated hemoglobin levels; however, the frequency of hypoglycemic episodes was unchanged. His endocrinologist has ruled out coexisting illnesses, including celiac disease and Addison's disease, as causes of poor glycemic control and wonders whether a trial of insulin-pump therapy is appropriate. Since the endocrinologist has little experience with this type of therapy himself, he refers the patient to a center with a specialized insulin-pump clinic.

THE CLINICAL PROBLEM

It is now well established that the serious microvascular complications of diabetes are linked to the duration and severity of hyperglycemia[1]; there have therefore been renewed efforts to help patients achieve near-normal blood glucose levels. The mainstay of current management of type 1 diabetes is "physiological insulin replacement," the main example of which is the practice of administering multiple daily injections of insulin.[2,3] Several organizations have set targets for glycemic control; for example, the American Diabetes Association recommends a general goal for glycated hemoglobin levels of less than 7%, though it recommends less stringent targets for some persons. However, in everyday clinical practice, it is widely recognized that such targets are easier to set than to achieve.[4] In a Scottish registry of 24,750 patients with type 1 diabetes,[5] only 7% had a glycated hemoglobin level of less than 7%, and in an Australian survey of patients with type 1 diabetes,[4] 13% had a glycated hemoglobin level of less than 7%.

As glycemic control improves with intensified insulin regimens, the frequency of hypoglycemia tends to increase.[1,6] Hypoglycemia is the cause of considerable stress and anxiety, impaired well-being, and poor quality of life in patients with type 1 diabetes, and 35 to 40% of patients with type 1 diabetes regularly have an

episode of severe hypoglycemia (an episode necessitating third-party assistance).[7-9] About 25% have blunting of the symptoms of hypoglycemia — known as hypoglycemia unawareness — and such patients have a risk of severe hypoglycemia that is increased by a factor of up to 6.[7-9] Hypoglycemia has been called the single greatest barrier to achieving and maintaining good glycemic control in patients with diabetes.[7]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

One reason for continued poor glycemic control in patients with type 1 diabetes is the erratic absorption and action of subcutaneously injected insulin,[10] which lead to unpredictable swings in blood glucose concentrations, and those swings, in themselves, are associated with elevated glycated hemoglobin levels[11] and hypoglycemia[12,13] (Fig. 1). It is likely that patients with high variability in glycemic levels maintain an elevated glycated hemoglobin level because they fear that hypoglycemia will occur more frequently or will be more severe if glycemic levels are reduced.[11]

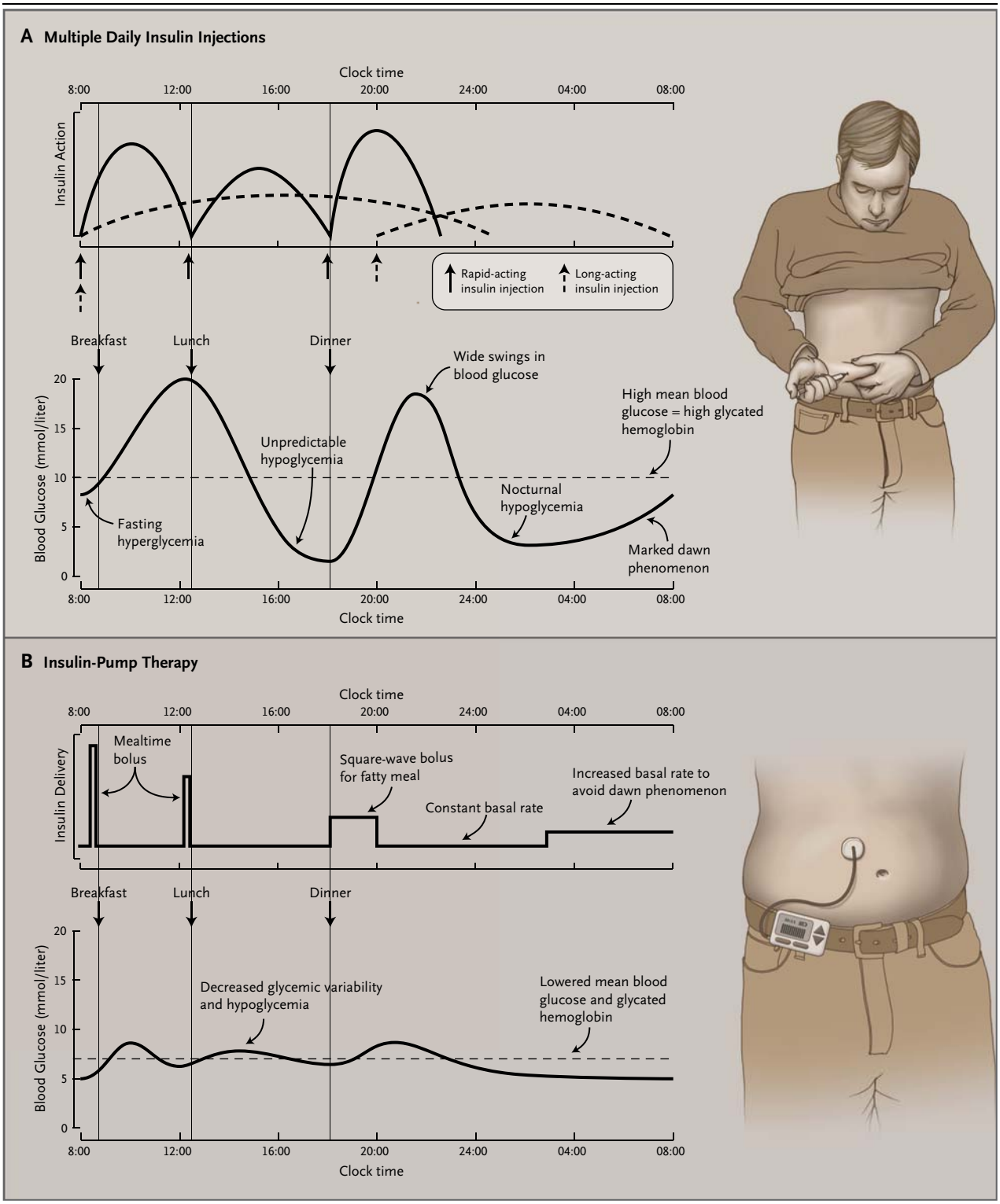
Another reason for continued poor glycemic control is that the dose of long-acting insulin analogues cannot be modulated after injection — for example, to provide greater insulin delivery from the previously injected depot in the prebreakfast hours, in order to counter the increase in blood glucose levels at that time of day ("dawn phenomenon").[14] At meals, errors in estimating the size and composition of the meal and in the timing and magnitude of the preprandial insulin dose can cause excessive hyperglycemia or late hypoglycemia. Adjustment of the insulin dose to account for exercise is daunting for many patients. The frequency of hypoglycemia unawareness and the risk of subsequent hypoglycemia are highest among patients who have had hypoglycemia most frequently in the past.[7-9] Finally, nonadherence to recommended therapy is a contributor to poor control in a substantial number of patients.[15]

Insulin-pump therapy, or continuous subcutaneous insulin infusion, was introduced more than 30 years ago[16,17] as a procedure for improving glycemic control in patients with type 1 diabetes by mimicking the insulin-delivery patterns that are present in persons without diabetes. A portable pump infuses rapid-acting insulin at a slow basal rate, 24 hours a day, through a fine cannula implanted in the subcutaneous tissue, with patient-activated insulin boosts (boluses) administered at mealtimes (Fig. 1). With insulin pumps in current use, the basal rate can either be altered on demand or preset to change at any time (e.g., during the night), and an onboard bolus calculator can advise the patient regarding the appropriate insulin dose at mealtime, as estimated on the basis of carbohydrate intake, premeal and target blood glucose levels, insulin sensitivity, and a calculation of the insulin remaining since the previous bolus.[18] Currently available pumps also have the capability for downloading data to a computer.

Insulin-pump therapy can improve glycemic control in patients with type 1 diabetes because it can reduce the within-day and between-day glycemic variability that is seen with insulin injections.[11,19,20] This effect may be related to the smaller subcutaneous depot of insulin during pump therapy (about 1 unit) and the low coefficient of variation for absorption during the basal-rate infusion — about ±3%, as compared with about ±50% for a large dose of injected isophane insulin.[21] The reduction in glycemic fluctuations allows patients to reduce glycated hemoglobin levels without increasing the risk of hypoglycemia.[11] Insulin-pump therapy may also lessen the problems of glycemic control associated with injections because it allows for more flexible, preprogrammable basal insulin rates and extended-wave insulin profiles that can reduce the risk of hyperglycemia after fatty meals[22]; because it includes a bolus calculator[23]; and because it includes the capability for computer downloads, which may identify control problems and aid in the adjustment of doses.[24] In addition, one may speculate that the increased flexibility of diabetes management and the improved feeling of well-being in patients who have an insulin pump[25] may increase adherence to intensified therapy.

CLINICAL EVIDENCE

Several meta-analyses of randomized, controlled trials of glycemic control with multiple daily insulin injections as compared with insulin-pump therapy have shown that mean glycated hemoglobin levels are significantly lower with insulin-pump therapy — with a mean difference of about 0.3 to 0.6% between treatments — and this reduction in gly-



cated hemoglobin levels is accompanied by a 10 to 20% reduction in the dose of insulin.[26-29] Among patients who switch from insulin injections to insulin-pump therapy, the most important determinant of the benefit of pump therapy with respect to glycemic control is the baseline glycated hemoglobin level, with the greatest effect seen in patients with the worst control at baseline.[11,28,30]

Figure 1 (facing page). Clinical Problems Associated with Multiple Daily Insulin Injections and the Insulin-Pump Solution.

Multiple daily insulin injections (Panel A) involve the injection of rapid-acting insulin (usually a monomeric analogue) before main meals and the injection of long-acting insulin (often analogue) once or twice daily (upper graph). Some patients have poor glycemic control (lower graph) despite the best efforts, with wide swings in blood glucose concentrations, frequent unpredictable hypoglycemia (including at night), an increase in blood glucose levels at dawn ("dawn phenomenon"), fasting hyperglycemia, and an elevated glycated hemoglobin level. Insulin-pump therapy (Panel B) consists of a constant but variable basal infusion of insulin (usually monomeric rapid-acting insulin) from a portable pump. The rate can be preset to increase or decrease on the basis of the patient's insulin requirements at that time of the day. Patient-activated insulin boluses at meals can be administered over a short period of time or as an extended square wave.

For example, the expected mean decrease in the glycated hemoglobin level is about 2 percentage points when the baseline glycated hemoglobin is 10%, whereas it is 0 percentage points when the baseline glycated hemoglobin is 7%.[11]

In a 2008 meta-analysis, the frequency of severe hypoglycemia was compared among patients receiving insulin-pump therapy and those receiving multiple daily insulin injections; the selected trials had a duration of 6 months or more, were published between 1996 and 2006 (when monomeric insulin was used in the pump), and included a study population that had a high initial rate of severe hypoglycemia. The meta-analysis showed that the frequency of severe hypoglycemia was significantly higher with multiple daily insulin injections than with insulin-pump therapy (rate ratio, 4.19; 95% confidence interval, 2.86 to 6.13).[28] The greatest reduction was seen among patients who had had the greatest number of episodes of severe hypoglycemia while they were receiving injection therapy. Among these patients, the rate of severe hypoglycemia was higher by a factor of about 30 with multiple daily insulin injections than with insulin-pump therapy.

Several trials have also evaluated quality of life among patients receiving insulin-pump therapy, with the use of a variety of measures. Although the findings differ across trials and a meta-analysis was not appropriate because of the use of different scales, a Cochrane review concluded that in many studies, pump therapy was preferred over multiple-dose insulin injections with respect to treatment satisfaction, quality of life, and perception of general and mental health.[29]

CLINICAL USE

Most people with type 1 diabetes can achieve acceptable control with multiple daily insulin injections when this therapeutic approach is applied sufficiently rigorously. It is therefore best to reserve the use of insulin-pump therapy for patients who have indications for which there is robust evidence for benefit (Table 1). In adults, these indications generally include poor control of hyperglycemia or disabling hypoglycemia, despite best efforts to achieve glycemic control with multiple daily insulin injections, although the specific criteria for these indications vary. For example, the U.K. National Institute for Health and Clinical Excellence (NICE) recommends consideration of insulin-pump therapy for patients with persistent glycated hemoglobin levels of 8.5% or higher,[31] whereas the Société Francophone du Diabète uses a threshold of 7.5% or higher.[32]

Although the same indications generally apply to children,[33] many pediatricians consider multiple daily insulin injections to be impractical or inappropriate for some children, because the children may be unable or unwilling to inject insulin at school and may need assistance from parents during the day. Some experts therefore suggest that children may be considered for pump therapy without having first failed to have adequate glycemic control with insulin injections. Particular challenges in the treatment of adolescents, with respect to both multiple daily insulin injections and insulin-pump therapy, include nonadherence, insulin resistance, and changing activity and sleep patterns. Though these variables are often managed more effectively with pump therapy than with multiple daily insulin injections,[34] some studies have shown that teenagers are the population that is most likely to have elevated glycated hemoglobin levels while receiving insulin-pump therapy and subsequently to discontinue the treatment.[35]

Insulin-pump therapy may be used during pregnancy.[36-38] However, the consequences of ketoacidosis during pregnancy (for example, if pump failure were to occur) are of particular concern. Nonetheless, it is reasonable to apply the above criteria for initiating pump therapy to pregnant women also, but with adjustment for

Table 1. Suggested Indications for Initiation of Insulin-Pump Therapy in a Patient with Type 1 Diabetes.

Continued elevated glycated hemoglobin levels despite best attempts with multiple daily insulin injections (with insulin-pump therapy shown to be cost-effective when baseline glycated hemoglobin levels are ≥8.5%, although the threshold may differ among national guidelines)*
Continued disabling hypoglycemia (in the judgment of the physician, since the definition of hypoglycemia rate or "disabling" hypoglycemia has not been firmly established), despite best attempts with multiple daily insulin injections*
Among children, elevated glycated hemoglobin level and disabling hypoglycemia while receiving insulin-injection therapy, as above, but also when, in the judgment of the physician, multiple daily insulin injections are considered to be inappropriate or impractical*
In the first trimester of pregnancy or before conception, when target glycated hemoglobin levels (<6.1%, or target levels specified in national guidelines) cannot be achieved without disabling hypoglycemia

* Multiple daily insulin injections involve injection of long-acting insulin analogues, frequent self-monitoring of blood glucose levels, structured patient education including carbohydrate counting and adjustment of insulin doses, and frequent contact with a multidisciplinary team of health care professionals.

the lower target levels of glycated hemoglobin that are needed during pregnancy.

Insulin-pump therapy should be initiated by a specialized hospital team comprising a physician, a diabetes nurse, and a dietitian trained in pump procedures. Initiation of pump therapy by primary care physicians is not recommended. It is important for the patient to be willing and motivated to use the insulin pump. The necessary commitments include frequent self-monitoring of blood glucose levels (four to six times daily), carbohydrate counting (adjustment of the insulin dose according to the estimated amount of carbohydrate in an intended meal), and working with the pump team to learn pump procedures. Starting insulin-pump therapy is generally contraindicated when a clinical team that specializes in this treatment is not available, when the patient is unwilling or unable to use the pump, or when the patient has major psychiatric problems.

Commercially available insulin pumps contain a reservoir that holds about 200 to 300 units of insulin, a battery with an effective life of several weeks, and electronic controls for the operation of the pump. Pumps usually have a display screen and controls to allow the user to enter information on dose and time. Most pumps deliver insulin through a flexible plastic tube, typically 60 or 110 cm in length and terminating in a Teflon cannula or stainless-steel needle, which is inserted into the subcutaneous tissue. The cannula may be implanted manually or automatically with the use of a spring-loaded device. One currently available pump is "tubeless," with the cannula integrated into the pump and a hand-held controller that is used to adjust rates. Other small "patch pumps" of this type, in which the pump is attached to the body with an adhesive patch (some including a remote-control device), are in development.

Monomeric, rapid-acting insulin analogues (aspart, lispro, or glulisine) are now considered to be the insulins of choice for pumps. For selecting the initial basal rate, the total daily injected dose is calculated and then is usually reduced by 20%. The basal rate is then calculated as 50% of that value; initially, only one rate is used for the entire 24-hour period, with varying rates introduced later. The overnight rate should be adjusted to maintain the prebreakfast blood glucose concentration in the target range. Carbohydrate counting is used to determine the bolus dose before a meal, which is based on the carbohydrate content of the intended meal; the patient's insulin sensitivity at meals ("insulin-to-carbohydrate ratio"); and a correction dose that is based on the blood glucose level before the meal, how far that level deviates from the target blood glucose level, and the insulin sensitivity factor. There are formulas that can be used to estimate the insulin-to-carbohydrate ratio (e.g., 500÷total daily insulin dose=grams of carbohydrate for each unit of insulin) and the insulin sensitivity factor (100÷total daily insulin dose=blood glucose lowering [in millimoles per liter] for each unit of insulin; this calculation is also used to correct unexplained hyperglycemia between meals). When the blood glucose is expressed in milligrams per deciliter, the insulin sensitivity factor is calculated as 1800÷total daily insulin dose. Many patients now use bolus calculators to estimate insulin doses before meals.

The anterior abdominal wall is the most common infusion site; the outer thighs, arms, hips,

and buttocks can be used but generally have slower insulin absorption. Areas of broken skin, lipodystrophy, or scarring should be avoided. The infusion cannula should be changed every 2 to 3 days and rotated to a new anatomical site — just as the site of insulin injections should be varied — to avoid lipohypertrophy. Keeping the same infusion set in place for longer than 3 days is associated with deterioration in glycemic control and an increased risk of infection at the site.

After an initial start-up phase of approximately 6 months, when clinic visits or contact with health care professionals may be more frequent, most patients who are receiving insulin-pump therapy do not need to be followed in the outpatient clinic more often than was necessary when they were receiving multiple daily insulin injections — approximately every 6 months. When patients receiving insulin-pump therapy are admitted to the hospital as inpatients for emergency or elective treatments and investigations, most prefer to continue receiving pump therapy; however, since the hospital staff may be inexperienced with continuous subcutaneous insulin infusion, advice from the local insulin-pump team and adherence to specific insulin-pump protocols are strongly recommended.[39]

Continuous subcutaneous insulin infusion is more expensive than multiple daily insulin injections: insulin pumps cost about $5,000 to $7,000, depending on the manufacturer and the country of purchase, with additional costs (about $2,500 per year) for pump supplies (infusion sets, reservoirs, and batteries) and for staff time and training. Cost-effectiveness studies[31,40-42] suggest that the incremental cost-effectiveness ratio for insulin-pump therapy as compared with insulin-injection therapy is about $25,000 to $55,000 per quality-adjusted life-year, indicating that insulin-pump therapy may be considered to be cost-effective.

About 20% of patients who are receiving insulin-pump therapy continue to have problematic hypoglycemia or hyperglycemia.[43] Such patients may have further improvement with the addition of continuous glucose monitoring.[44] For this approach, a needle-type or wire-type glucose sensor is implanted subcutaneously and replaced about every 5 to 7 days. The sensor measures interstitial glucose concentrations on a nearly continuous basis. Data are transmitted wirelessly to a portable meter or (in the case of some models) to an insulin pump for display of glucose values and trends.[45]

In consultation with the patient, insulin-pump therapy should be discontinued if there is no sustained improvement in glycated hemoglobin levels or the frequency or severity of hypoglycemia, if psychiatric or other contraindications emerge after the initiation of pump treatment, or, possibly, if the patient has recurrent skin infections. In addition, pump therapy should, of course, be discontinued if the patient wishes to return to the regimen of multiple daily insulin injections. However, at most centers the rate of discontinuation is only about 5% or less.

ADVERSE EFFECTS

Because there is a smaller subcutaneous depot of insulin at any time with the insulin pump, there is a greater risk that ketoacidosis will develop with insulin-pump therapy than with multiple daily insulin injections if, for example, insulin delivery is interrupted because of a pump malfunction or insulin demand is increased because of an intercurrent illness. However, in practice, the frequency of ketoacidosis is similar with the two treatments,[25,31,46,47] probably because regular self-monitoring of blood glucose levels and a prompt response to hyperglycemia are key parts of modern pump practice. Among patients at experienced centers, the frequency of ketoacidosis can be lower with insulin-pump therapy than with multiple daily insulin injections.[47] Localized skin infections at the infusion site occasionally occur with insulin-pump therapy, but they are rarely serious.[47] Current pumps are robust and reliable, but malfunctions can still occur.[47]

Patients and health care professionals need a checklist of possible reasons for unexplained hyperglycemia, with the list including problems with the cannula (kinked, blocked, or leaking cannula or failure of the cannula to prime after change), problems at the infusion site (infection, lipohypertrophy, dislodgment of the infusion set, or a set that has been left in place for longer than 3 days), malfunction of the pump (low battery, inactive insulin or insulin past the expiration date, or mechanical or electrical failure with alarms), and patient-associated issues (missed bolus, incorrect basal rates, overcorrection of hypoglycemia, illness, use of drugs such as steroids, or menstruation). Similarly, a checklist for unexplained hypoglycemia may include incorrect bolus or basal rates, performance of exercise without consumption of extra carbohydrates or

reduction of the bolus or basal rate, delayed effect of exercise, target levels that are set too low, consumption of alcohol, gastroparesis, and inadequate self-monitoring of blood glucose levels.

AREAS OF UNCERTAINTY

It is unclear to what extent structured diabetes education programs such as the Dose Adjustment for Normal Eating (DAFNE) program[48] and more enthusiastic input from health care professionals would lessen the proportion of patients who have elevated glycated hemoglobin levels and hypoglycemia while they are receiving insulin-injection therapy and who are thus candidates for insulin-pump therapy. There are relatively few randomized, controlled trials of insulin-pump therapy as compared with multiple daily insulin injections of the long-acting analogue insulins glargine and detemir,[28,49] and more research into these regimens as part of DAFNE-type programs would be helpful.

The expansion of patient groups selected for insulin-pump therapy beyond those with grossly elevated glycated hemoglobin levels and frequent episodes of hypoglycemia is also the subject of debate. The enhanced quality of life noted by many patients who are receiving pump therapy includes improvements in lifestyle flexibility, energy, well-being, family relationships, and the ability to perform effectively and confidently at work. These aspects are not easily captured by cost-effectiveness studies. Poor quality of life is mentioned in some guidelines as a criterion for selection of insulin-pump therapy (see below), but it is likely that increasing attention will be paid in the coming years to lifestyle issues and personal preference as indications for pump therapy.

GUIDELINES

The NICE guidelines recommend insulin-pump therapy for adults when, despite the best attempts to achieve target blood glucose levels with multiple daily insulin-injection therapy, disabling hypoglycemic episodes continue to occur or glycated hemoglobin levels remain high (≥8.5%) and for children younger than 12 years of age whenever multiple daily insulin injections are considered to be impractical or inappropriate.[31] The guidelines for insulin pumps from the American Association of Diabetes Educators notably also include "frequent and unpredictable fluctuations in blood glucose" and "patient perceptions that diabetes management impedes the pursuit of personal or professional goals" as criteria for starting pump therapy,[50] and other guidelines cite similar indications.[32] However, many consider these indications to be inadequately defined and believe that they should be used as criteria only if there is strong evidence that they have been associated with hyperglycemia or hypoglycemia.

RECOMMENDATIONS

The patient described in the vignette has been unable to achieve acceptable glycemic control with multiple daily insulin injections — despite having recently attended a diabetes education course — because of disabling, severe hypoglycemia. The hypoglycemia is probably due in part to unpredictable glycemic fluctuations, which have also prevented the lowering of glycated hemoglobin to target levels. If, after undergoing an assessment at a specialized center and discussing the options with a team that is experienced in insulin-pump therapy, the patient is willing and able to undergo a trial of such therapy, this should be arranged. It is to be expected that the frequency of severe hypoglycemia will be reduced and glycated hemoglobin levels will be lowered and that the patient's quality of life will improve. His body-mass index may also be reduced, since there will be less need for him to eat in order to avoid hypoglycemia, and improved control may be attained with a lower dose of insulin.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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