CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will prescribe insulin appropriately to patients who have type 2 diabetes

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Insulin treatment for type 2 diabetes: When to start, which to use

ABSTRACT

In type 2 diabetes mellitus, oral hypoglycemic agents and analogues of glucagon-like peptide-1 provide adequate glycemic control early in the disease. Insulin therapy becomes necessary for those with advanced disease. Further, some experts recommend electively starting insulin therapy in early diabetes. This review addresses practical approaches to insulin therapy, particularly when it is indicated and which regimen to use.

KEY POINTS

Whether to start insulin therapy and which regimen to use depend on a number of factors, including the patient's acceptance and willingness to adhere to the therapy.

A common way to start is to add a once-daily dose of a long-acting insulin at bedtime (basal insulin) to the patient's antidiabetic regimen.

Basal regimens do not control postprandial hyperglycemia very well. Another option is to take a long-acting (basal) insulin along with a rapid-acting (prandial or bolus) insulin before meals. Multiple formulations of premixed insulins are available and are convenient to use among new users.

Basal-bolus regimens, which involve injections of rapid-acting insulin before meals and long-acting insulin at bedtime, are gaining popularity. Their cost and the number of injections may affect patient acceptance of this treatment.

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Many patients with type 2 diabetes eventually need insulin, as their ability to produce their own insulin from pancreatic beta cells declines progressively.[1] The questions remain as to when insulin therapy should be started, and which regimen is the most appropriate.

Guidelines from professional societies differ on these points,[2,3] as do individual clinicians. Moreover, antidiabetic treatment is an evolving topic. Many new drugs—oral agents as well as injectable analogues of glucagon-like peptide-1 (GLP1) and insulin formulations—have become available in the last 15 years.

In this paper, I advocate an individualized approach and review the indications for insulin treatment, the available preparations, the pros and cons of each regimen, and how the properties of each type of insulin influence attempts to intensify the regimen.

Coexisting physiologic and medical conditions such as pregnancy and chronic renal failure and drugs such as glucocorticoids may alter insulin requirements. I will not cover these special situations, as they deserve separate, detailed discussions.

WHEN SHOULD INSULIN BE STARTED? TWO VIEWS

Early on, patients can be adequately managed with lifestyle modifications and oral hypoglycemic agents or injections of a GLP1 analogue, either alone or in combination with oral medication. Later, some patients reach a point at which insulin therapy becomes the main treatment, similar to patients with type 1 diabetes.

The American Diabetes Association (ADA), in a consensus statement,[2] has called

Caveats about clinical trials of insulin therapy

Clinical trials of insulin should always be interpreted with caution, as they share several limitations.

They are all open-label. This is their most crucial limitation—they cannot be single-blinded, let alone double-blinded. Once an insulin is shown to be effective in lowering glucose in phase 1 and 2 clinical trials, it should be compared with other insulins on the market to show noninferiority. Use of placebo is not ethical in phase 3 trials, and even for phase 1 and 2 if patients have significant hyperglycemia.

The open-label design of insulin trials make it difficult to prevent the influence of the investigators' bias, their clinical experience in treating diabetes, and the study protocol on outcomes.

Their protocols differ in how the dosage is titrated. This is a crucial confounding factor that is difficult to account for. This explains some of the contradictory results among studies. In fact, comparative studies test at least two medications and two titration protocols. If one treatment is found to be superior to the other, it may be that the medication is superior, the protocol is superior, or both. Likewise, inferiority or noninferiority of a regimen may relate to the interaction between the medications used and the study protocol.

Patient adherence affects outcomes. Adherence to a study medication should be considered as an outcome per se rather than a confounding variable. Patient satisfaction with the treatment is a main element of adherence, which is a key for the success of any treatment. In fact, patient satisfaction and adherence are measured outcomes in most studies.

Multicenter studies and reproducible outcomes ameliorate these limitations. Findings confirmed by other trials (ie, that are reproducible) should be given more weight.

for using insulin early in the disease if lifestyle management and monotherapy with metformin (Glucophage) fail to control glucose or if lifestyle management is not adequate and metformin is contraindicated. The ADA's goal hemoglobin A_{1c} level is less than 7% for most patients.

The American Association of Clinical Endocrinologists (AACE) and **the American College of Endocrinology** (ACE), in another consensus statement, use an algorithm stratified by hemoglobin A_{1c} level, in which insulin is mostly reserved for when combination therapy fails.[3] Their goal hemoglobin A_{1c} level is 6.5% or less for most patients.

Comment. Both consensus statements make exceptions for patients presenting with very high blood glucose and hemoglobin A_{1c} levels and those who have contraindications to drugs other than insulin. These patients should start insulin immediately, along with lifestyle management.[2,3]

Both consensus statements give priority to safety. The AACE/ACE statement gives more weight to the risk of hypoglycemia with insulin treatment, whereas the ADA gives more weight to the risk of edema and congestive heart failure with thiazolidinedione drugs (although both insulin and thiazolidinediones cause weight gain) and to adequate validation of treatments in clinical trials.

Ongoing clinical trials may add insight to this issue. For example, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study is investigating the effects of the long-acting insulin glargine (Lantus) in early diabetes with regard to glycemic control, safety, and cardiovascular outcomes.[4] This study is expected to end this year (2011). The safety of alternative treatment options is also under investigation and scrutiny. In the interim, individualized treatment should be considered, as we will see below.

For most patients, I believe a goal hemoglobin A_{1c} < 7% is reasonable

TABLE 1

Definition of severe hyperglycemia

Fasting glucose level > 250 mg/dL

Random glucose level consistently > 300 mg/dL

Hemoglobin A_{1c} level > 10%

Ketonuria

Symptomatic diabetes

Polyuria, polydipsia, weight loss

BASED ON INFORMATION IN 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.

MY VIEW: AN INDIVIDUALIZED APPROACH

The decision to start insulin therapy should be made individually, based on several factors:

- Whether the patient is willing to try it
- The degree of hyperglycemia
- How relevant the potential side effects of insulin are to the patient compared with those of other hypoglycemic agents
- Whether oral hypoglycemic agents with or without GLP1 analogues are expected to provide the desired benefit
- The patient's work schedule and lifestyle factors
- Cost
- The availability of nurses, diabetes educators, and others to implement and follow the insulin treatment.

Insulins for basal therapy: glargine (Lantus), detemir (Levemir), NPH (Humulin N and Novolin N)

Will patients accept insulin?

Factors that affect whether patients comply with a treatment include the number of pills or injections they must take per day, how often they must check their blood glucose, adverse effects, lifestyle limitations caused by the treatment (especially insulin), and cost. Most patients feel better when their glucose levels are under good control, which is a major motivation for initiating and adhering to insulin. The anticipated reduction of diabetic complications further enhances compliance.

Education promotes compliance. Patients need to know that type 2 diabetes tends to progress and that in time their treatment will have to be intensified, with higher doses of their current drugs and new drugs added or substituted, possibly including insulin. This information is best given early, ie, when the diagnosis is made, even if hyperglycemia is mild at that time.

With newer insulin preparations and delivery devices available, more patients are finding insulin treatment acceptable.

The glycemic goal should be individualized

The key issue is glycemic control. If glycemic control is worsening or if the hemoglobin A_{1c} level remains above the goal, then the treatment strategy should be readdressed.

In general, one should try to achieve the best possible glycemic control with the few est adverse effects. Adequate dietary management with a regular meal schedule and predictable carbohydrate intake for each meal helps to avoid or at least minimize the two most important adverse effects of insulin, ie, weight gain and hypoglycemia.

For most patients, I believe a goal hemoglobin A_{1c} level of less than 7% is reasonable.[2] For others, a less stringent goal might be more appropriate, such as 7.5%. Several factors affect this decision, including whether the patient is willing to follow a complex insulin regimen (such as a basal-bolus regimen), his or her work schedule, other lifestyle factors, the duration of diabetes, the type or types of insulin used, coexisting medical conditions, the frequency of hypoglycemia, unawareness of hypoglycemia, age, prognosis, life expectancy, and cost.[5]

If hyperglycemia is severe (TABLE 1),[2] the goal might not be clear when insulin therapy is started. It should become obvious with ongoing follow-up.

Previously untreated patients presenting with severe hyperglycemia are a heterogeneous group. Many of them have had diabetes for a relatively short time and were recently diagnosed. These patients are likely to safely achieve near-normal glycemic control. Some of them might be adequately treated with oral hypoglycemic agents; if insulin is used, transitioning from insulin to oral hypoglycemic agents may be feasible.[2]

Some untreated patients may have had diabetes for several years and have advanced disease and therefore might be more difficult to treat. Only 21 (57%) of 37 previously untreated patients intensively treated with insulin reached the goal fasting glucose level of less than 126 mg/dL in one study.[6] The only way to evaluate the feasibility of achieving near-normal glycemia safely is by following the patient's progress over time.

The patient's glycemic goal should be reevaluated periodically and may need to be adjusted over time, based on changes in any of the factors discussed above.

Risk of hypoglycemia

The goal should be looser in difficult-to-treat patients, ie, those with frequent hypoglycemia and decreased awareness of hypoglycemia.

Patients with advanced diabetes whose glucose levels continue to fluctuate widely after lifestyle management and the insulin regimen have been addressed should also have a looser goal. These fluctuations of glucose levels are surrogate markers for the degree of insulin deficiency. Attempting to achieve near-normal glycemic levels in this situation would be associated with a higher risk of hypoglycemia.

A higher risk of hypoglycemia and its complications (eg, falling and accidents, especially among operators of heavy machinery, construction workers, and drivers) is another reason for adopting a relaxed goal of glycemic control.

TABLE 2 summarizes risk factors for hypoglycemia.[5,7–9] Relationships between insulin dosage, hemoglobin A_{1c} level, and the risk of hypoglycemia have not been consistent among studies.[8] Several important risk factors for hypoglycemia are not reported in prospective clinical studies because of exclusion criteria in those studies.

TABLE 2

Risk factors for hypoglycemia

Risk factors identified in prospective clinical trials
Advanced age
Decreased awareness of hypoglycemia
Duration of insulin therapy
History of hypoglycemia
History of microvascular complications
History of smoking
Intensive therapy and using two or more oral hypoglycemic agents
Long diabetes duration
Lower body mass index

Factors related to lifestyle
Alcohol use, especially with a low-carbohydrate meal or no meal
Less food intake, missed or delayed meals, erratic food intake
Vigorous exercise without carbohydrate compensation

Factors related to coexisting medical conditions
Alcoholism
Conditions that can mask or mislead the diagnosis of hypoglycemia: dementia, depression, sleep disorder, cerebrovascular disorder, myocardial infarction
Impaired cognitive function, dependence or isolation that could lead to delay in receiving treatment for hypoglycemia
Liver failure
Malnutrition, malabsorption, interruption of nutrition (including tube feeding)
Polypharmacy, including both drug interactions and noncompliance
Renal insufficiency
Sepsis, malignancies
Untreated or undertreated endocrine disorders
Adrenal insufficiency
Hypopituitarism
Hypothyroidism

BASED ON INFORMATION IN AMERICAN DIABETES ASSOCIATION. STANDARDS OF MEDICAL CARE IN DIABETES—2010. DIABETES CARE 2010; 33(SUPPL 1): S11–S61, ZOUNGAS S, PATEL A, CHALMERS J, ET AL; ADVANCE COLLABORATIVE GROUP. SEVERE HYPOGLYCEMIA AND RISKS OF VASCULAR EVENTS AND DEATH. N ENGL J MED 2010; 363:1410–1418, AND CRYER PE. CHAPTER 19. HYPOGLYCEMIA. IN: JAMESON JL, EDITOR. HARRISON'S ENDOCRINOLOGY. MCGRAW HILL, 2006:355–363.

ADDING BASAL INSULIN TO ORAL HYPOGLYCEMIC THERAPY

When glycemic control worsens or is not adequate despite the use of oral hypoglycemic agents, often the next step is to add basal insulin therapy, ie, once-daily doses of a long-acting insulin.

NPH, detemir, or glargine?

Most often, glargine or detemir (Levemir) insulin is used. Detemir can also be given twice daily if needed. If cost is a concern, neutral protamine Hagedorn (NPH, Humulin N, Novolin N) insulin once daily at bedtime or twice daily is a reasonable alternative.

Costs of basal insulins are $22 to $50 per 1,000-unit vial for NPH, $70 to $90 per 1,000-unit vial for detemir and glargine, and $170 to $200 for a box of five detemir or glargine pens (containing 1,500 units total). Complicating

this issue, vials should not be used for more than 1 month, and thus, the cost of vials vs pens depends on dosage.

Detemir vs NPH. In a trial in patients with inadequately controlled type 2 diabetes who had never taken insulin before and who were taking one or more oral hypoglycemic drugs, the addition of detemir insulin once daily or NPH at bedtime resulted in similar improvements in hemoglobin A_{1c} (a decrease of about 1.5%).[10]

Detemir had several advantages over NPH. First, the incidence of nocturnal hypoglycemia was 50% lower with detemir at bedtime than with NPH at bedtime, and 87% lower with detemir in the morning than with bedtime NPH.[10] In another trial,[11] the risk of hypoglycemia at any time of day was 47% lower with insulin detemir than with NPH, and the risk of nocturnal hypoglycemia was 55% lower.

The risk of nocturnal hypoglycemia is lower if detemir is taken in the morning than at bedtime, although the total frequency of hypoglycemic episodes is the same.[10] Therefore, another decision after starting basal insulin, based on the patient's glucose trends and frequency of hypoglycemic events, would be whether insulin should be taken in the morning or at bedtime.

The second advantage of detemir is that it causes less weight gain: 0.7 kg at 20 weeks with detemir at bedtime vs 1.6 kg with NPH at bedtime.[10]

Further, detemir insulin was associated with less within-subject variability in the fasting glucose level than with NPH when these insulins were used in a basal-bolus regimen.[12]

Hermansen et al[11] found that if the dosage of basal insulin was aggressively increased, 70% of patients achieved a hemoglobin A_{1c} target of less than 7% with either NPH or detemir insulin, with fewer hypoglycemic episodes in patients treated with detemir.

Therefore, adding basal insulin to oral therapy is adequate for many patients who are new to insulin. Many patients would need more, such as the addition of insulin before meals.

Glargine vs NPH. Compared with adding NPH, adding glargine to a regimen of oral hypoglycemic agents controls blood glucose levels better and with less fluctuation in glucose levels, a lower risk of hypoglycemia, and less weight gain.[13–15] These results were the same when using glargine with either metformin[13] or glimeperide (Amaryl).[14]

Glargine is usually given once daily at bedtime. One study suggested that giving it in the morning is more effective.[14]

Detemir vs glargine. Studies that compared detemir and glargine revealed more similarities than differences in their clinical benefits.[16,17] Both preparations effectively lower glucose levels and improve quality of life.[18]

Titrating the insulin regimen is a key in achieving adequate glycemic control. This includes teaching patients how to adjust their insulin, for example by increasing the dosage of glargine or detemir by 2 units every 4 to 7 days until adequate glycemic control is achieved, unless hypoglycemia becomes a barrier.

BASAL VS PRANDIAL INSULIN

Once-daily insulin injection is relatively convenient, but it comes with a limitation: it does not adequately control postprandial hyperglycemia. A solution is insulin before meals, ie, prandial insulin.

Rapid-acting insulins: lispro (Humalog), aspart (Novolog), glulisine (Apidra), regular (Humulin R and Novolin R)

Kazda et al[19] compared three regimens in patients not taking oral hypoglycemic agents: rapid-acting insulin lispro (Humalog) before each meal, a mix of 50% lispro and 50% protamine lispro (Humalog Mix 50/50) (the protamine delays its release) before each meal, and glargine at bedtime. The absolute change in hemoglobin A_{1c} was –0.3% in the glargine group, –1.1% in the lispro group, and –1.2% in the lispro mix group. The glargine group had better control of fasting glucose.

Similar advantages of better glycemic control and fewer nocturnal hypoglycemic episodes were seen in trials of a mixture of 25% lispro and 75% protamine lispro before meals compared with glargine insulin in patients on simultaneous treatment with oral hypoglycemic agents.[20,21] Buse et al[21] reported that more patients achieved a hemoglobin A_{1c} level below 7% with this lispro mix (47%) than with glargine (40%). The absolute difference in mean hemoglobin A_{1c} between the two groups was minimal, although it reached statistical

significance. As expected, weight gain was less in the glargine group.[21]

Kann et al[22] reported that glycemic control was also better with a mixture of 30% aspart and 70% protamine aspart (NovoLog Mix 70/30) twice a day along with metformin than with glargine insulin once a day along with oral glimepiride, a sulfonylurea. Further, in this study, weight gain was noted in the glargine-glimepiride group only.[22] Therefore, the advantage of less weight gain has not been always reproducible in glargine studies.

Comment. These studies point to the contribution of postprandial glucose to hemoglobin A_{1c}.[23–25] In patients with satisfactory glycemic control, the postprandial glucose level seems to be the major contributor to hemoglobin A_{1c}. When glycemic control worsens, the contribution of fasting glucose to hemoglobin A_{1c} increases.[23]

Premixed insulins (lispro mix and aspart mix) provide basal coverage and control postprandial hyperglycemia. Therefore, prandial premixed insulin therapy is expected to be superior to basal insulin therapy. Premixed insulin could be considered as a simplified basal-bolus regimen (see below).

The superiority of prandial (rapid-acting) insulin *alone* over basal insulin therapy, as seen in the study by Kazda et al,[19] has not been reproducible in other studies. For example, in one study, once-daily glargine resulted in a similar improvement in hemoglobin A_{1c}, a lower rate of hypoglycemic episodes, and greater patient satisfaction with treatment compared with lispro insulin before meals.[26] This issue remains debatable because all the trials have been open-label and thus are subject to limitations.

The main lesson is that either glargine or lispro monotherapy is a reasonable option and results in better glycemic control in patients for whom two oral hypoglycemic agents have failed. Further, both fasting and postprandial hyperglycemia are important to address. In patients with severe hyperglycemia, a combination of prandial and basal insulin may be indicated. One would expect neither basal nor prandial (bolus) insulin to be adequate in this situation.

In conclusion, adding basal insulin to oral hypoglycemic agents is a reasonable option in the advancement of diabetes therapy and has become a common way to introduce insulin. It is simple and less labor-intensive for patients and medical groups than a basal-bolus regimen. Patients usually find it acceptable. The future availability of an easy-to-deliver, safe, and effective prandial insulin may change the current treatment paradigm; several newer prandial insulins are under investigation.

In advanced diabetes, both prandial and fasting glucose levels are crucial to address. Some patients may need to be started on both basal and prandial insulin simultaneously, depending on their degree of hyperglycemia, the duration of diabetes, coexisting medical conditions, and the goal of glycemic control.

BASAL-BOLUS INSULIN REGIMENS

In the advanced stages of type 2 diabetes, as insulin deficiency worsens, patients need to start giving themselves injections of a rapid-acting insulin—regular, lispro, aspart, or glulisine (Apidra) before meals, in addition to once- or twice-daily basal insulin injections. Such a "basal-bolus" regimen could also be used for newly diagnosed patients presenting with severe hyperglycemia. In addition, some patients on basal insulin plus oral hypoglycemic drugs may develop contraindications to their oral drugs. Adding bolus insulin becomes the main option for these patients too.

If cost is an issue, NPH and regular insulin remain good options

For others, a basal-bolus regimen might be chosen purely because of cost. For example, a regimen of NPH and regular insulin (multiple daily injections or premixed) would be significantly less expensive than multiple oral hypoglycemic agents.

Currently, only a few classes of oral hypoglycemic drugs are available in generic formulations. For example, generic glimeperide and metformin cost as little as $4 to $12 per month, while the costs of brand-name oral hypoglycemic agents are in the range of $170 to $200 per month. In contrast, premixed NPH plus regular insulin such as Novolin 70/30 and Humulin 70/30 cost between $22 and $70 per vial.

A basal-bolus regimen should provide 50% of the total daily insulin in the form of basal insulin. A regimen of 50% basal and 50% bo-

lus seemed to provide better glycemic control than a regimen of 35% basal and 65% bolus in several studies.[27,28]

In patients already taking a single daily dose of basal insulin along with oral hypoglycemic agents, the dosage of basal insulin is usually raised gradually until adequate glycemic control is achieved. A main question is when to add prandial insulin. There is no clear cutoff for a basal insulin dosage at which prandial insulin should be added.

In the Treat-to-Target Trial,[29] almost 60% of patients achieved a hemoglobin A_{1c} level of 7% or less with the addition of either glargine or NPH insulin (basal insulin only) to oral hypoglycemic agents during 24 weeks of follow-up. As expected, glargine caused less nocturnal hypoglycemia. Fewer than half the patients who achieved a hemoglobin A_{1c} level less than 7% had no documented nocturnal hypoglycemia (33% of glargine-treated patients and 27% of NPH-treated patients).

Type 2 diabetes is progressive[1]; over time, patients treated with once-daily basal insulin often require multiple daily injections.

A basal-bolus insulin regimen should be 50% basal, 50% bolus

Adding prandial to basal insulin clearly results in better glycemic control and less glucose variability.[19,20,22,30–33] Two major factors in deciding to start prandial insulin are the degree of hyperglycemia and the patient's acceptance of multiple daily injections. The higher the blood glucose levels, the sooner prandial insulin should be added, especially if hyperglycemia is influencing the prognosis of a coexisting condition or a diabetic complication (eg, an infected foot ulcer).

Adding prandial insulin should be also considered if the dosage of basal insulin has progressively been increased and the hemoglobin A_{1c} level is not improving, especially if a patient has both inadequate glycemic control and frequent hypoglycemia, or if the morning glucose level is within the desired range (indicating there is no room for a further increase in the basal insulin dose) in association with inadequate control of hemoglobin A_{1c}.

What is the best basal insulin for a basal-bolus regimen?

Glargine and detemir were shown to be equally effective as the basal component of a basal-bolus regimen.[34,35] Findings were similar to those of studies comparing NPH, detemir, and glargine added, by themselves, to oral hypoglycemic agents. When possible, either glargine or detemir is favored because of less hypoglycemia and less weight gain than with NPH. Weight gain is the least with detemir.

Adding prandial insulin to a basal regimen

In general, whether to add prandial insulin can be decided on the basis of the patient's record of blood glucose monitoring. Insulin could be added before breakfast if the pre-lunch glucose level is elevated, or before lunch if the dinnertime blood glucose level is elevated, or before dinner if the bedtime blood glucose level is elevated—or a combination of these. Prandial insulin can be started at a low dose (4–6 units) and increased gradually.

For patients taking NPH at bedtime, adding another dose of NPH in the morning is a reasonable option for managing pre-dinner hyperglycemia (**FIGURE 1**).[2]

In the case of poor glycemic control on a high dosage of basal insulin, a reasonable first step would be to change the regimen to a basal-bolus regimen (about 50% basal and 50% bolus) with no change or a small decrease in the total daily dosage of insulin to avoid hypoglycemia. For example, in a patient on 80 units of glargine or detemir insulin who has inadequate control, the regimen could be changed to 35 units of either glargine or detemir and 10 to 12 units of lispro, aspart, or glulisine before each meal as the bolus component.

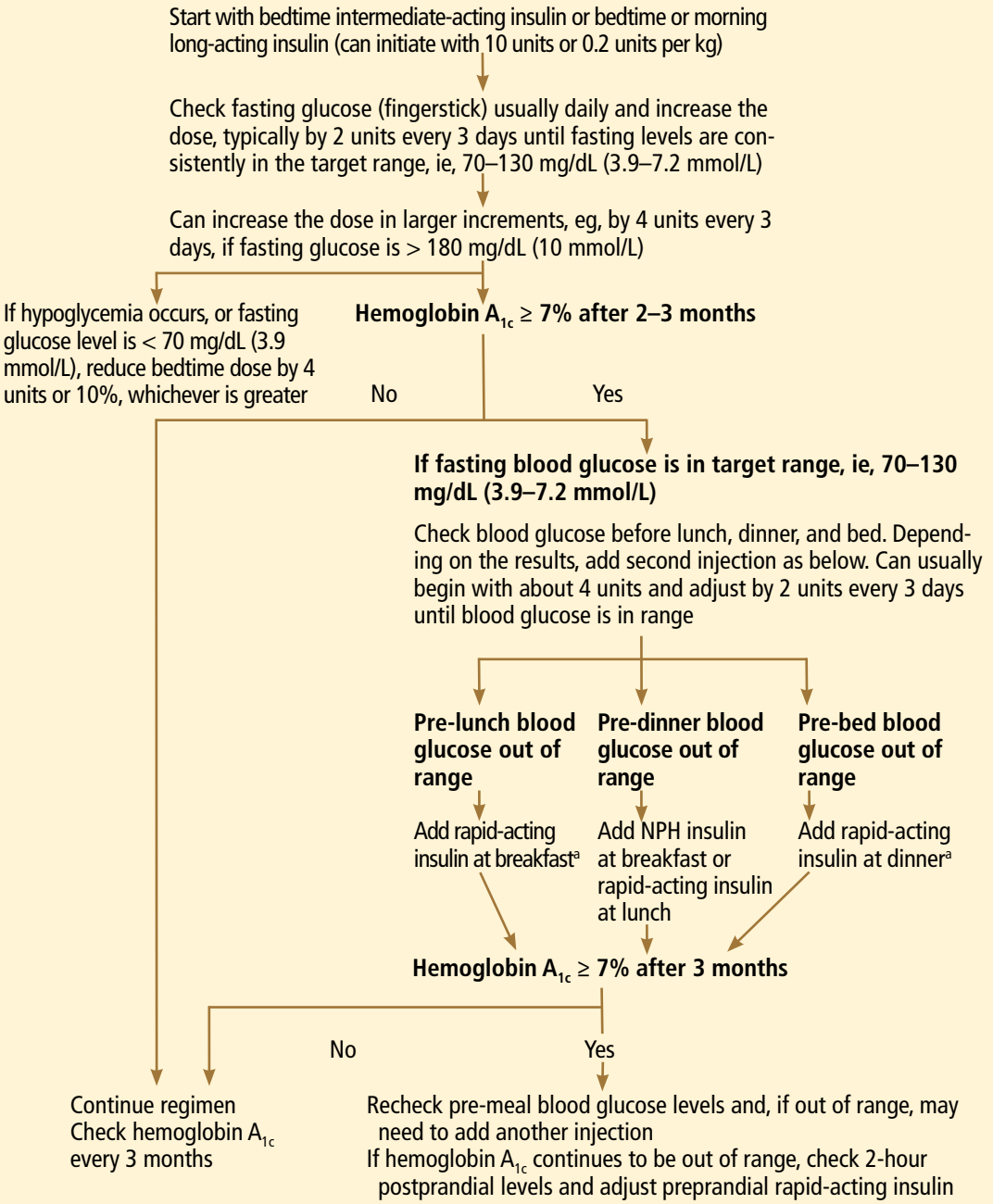
Further adjustments of the insulin dosage can be made according to the results of glucose monitoring before each meal and at bedtime. In all case scenarios, the insulin regimen should be re-evaluated routinely during the advancement of therapy from single daily injection of basal insulin to multiple daily injections. Redistribution of total insulin dosage to 50% basal and 50% bolus (divided into three doses before meals) should be considered for patients who continue to have fluctuations of glucose levels, inadequate control, or frequent hypoglycemia. This ratio seems to provide better control for most patients.[27,28]

Starting with a basal-bolus regimen

For patients new to insulin who are starting a basal-bolus regimen, a dosage based

Initiation and adjustment of insulin regimens

Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin.



[a]Premixed insulins are not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast, dinner, or both, if the proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available.

FIGURE 1

Rapid-acting insulin analogues control postprandial glucose levels better than regular insulin and cause less hypoglycemia

on total body weight could be considered. The requirements vary significantly based on dietary management, level of physical activity, stress (especially illnesses), use of oral hypoglycemic agents, and degree of hyperglycemia.

A lower dosage of insulin (0.2 units per kg) should be considered for people with mild stress, with milder hyperglycemia, or on treatment with oral hypoglycemic agents. Elderly patients and patients with renal or liver failure are at higher risk of hypoglycemia and should also receive a lower dosage of insulin, at least to start with.

Others could be started on a dosage of 0.3 to 0.5 units/kg. Fifty percent of the calculated dosage could be given as basal insulin and 50% given as bolus (divided into three doses, before meals). Subsequently, the dosage would need to be titrated on the basis of the record of glucose monitoring.

Choosing a prandial insulin

Rapid-acting insulin analogues (lispro, aspart, and glulisine) control postprandial glucose levels better than regular insulin and cause less hypoglycemia. Their pharmacokinetics enable them to be taken within a few minutes of the start of a meal, or even after the meal if the patient forgets to take an injection before the meal.

Glycemic control is harder to achieve with premixed insulin twice daily, mainly because of hypoglycemia

For example, in one study,[36] taking aspart immediately before the meal provided better glycemic control than taking regular insulin 30 minutes before meals. In a basal-bolus regimen, the use of aspart along with detemir resulted in glycemic control similar to that provided by twice-daily NPH and regular insulin, with less hypoglycemia.[37]

The dosage of prandial insulin can be adjusted according to the amount of carbohydrates in each meal (the insulin-to-carbohydrate ratio), as in patients with type 1 diabetes. This approach was associated with less weight gain.[38]

IS THERE STILL A ROLE FOR PREMIXED INSULIN PREPARATIONS?

Basal-bolus insulin regimens have gained popularity because the prandial doses can easily be adjusted according to carbohydrate intake, glucose level (on a sliding scale), variations in meal time, missed meals (eg, when having a procedure), and exercise. For example, the dose of prandial insulin can be reduced if the patient expects to exercise within 2 or 3 hours after the meal.

Some patients may not accept giving themselves four or five injections per day with a basal-bolus regimen. They may accept a simpler regimen, ie, giving themselves three injections of a premixed insulin per day, one before each meal.

Compared with a basal-bolus regimen, the possibility of achieving adequate glycemic control using lispro mix (50% lispro, 50% lispro protamine suspension) before meals seemed to depend on the goal of glycemic control. Its use in one study showed similar ability to achieve hemoglobin A_{1c} less than 7.5% compared with a basal-bolus regimen of glargine and lispro. For a goal hemoglobin A_{1c} level of less than 7%, the use of glargine and lispro was superior. The rate of hypoglycemia was similar with both strategies.[39] These findings imply that the goal hemoglobin A_{1c} should be more relaxed (< 7.5%) when using lispro mix (50% lispro) three times daily before meals.

Biphasic insulin aspart (a mix of aspart and protamine aspart) given three times daily provided similar improvement in glycemic control with no difference in the frequency of hypoglycemia compared with a basal-bolus regimen of NPH and aspart.[40] Further, the use of biphasic insulin aspart seemed to provide better glycemic control with less weight gain compared with premixed human insulin (70% NPH, 30% regular insulin).[41]

Therefore, simpler premixed insulin regimens remain reasonable options for selected patients who do not accept a more complex insulin regimen (basal-bolus) or cannot adhere to it for any reason, especially if premixed insulin is given before meals three times daily. In fact, recent studies have focused on comparing premixed insulin three times daily with basal-bolus regimens (detemir or glargine as basal insulin along with pre-meal insulin analogue).

Glycemic control is harder to achieve with premixed insulin twice daily, mainly because

of a higher frequency of hypoglycemia.[42] In Europe, the use of premixed insulin three times daily is a popular option, whereas in the United States, a twice-daily schedule has been more common.

COST VS CONTROL

Newer insulin analogues make insulin treatment safer and more accepted by patients. The availability of several options for insulin regimens allows individualization of the treatment according to the patient's acceptance, the safety profile, and the cost.

Patient selection and insulin titration are key issues in ensuring the achievement of adequate control with the fewest side effects. Lifestyle management (diet and physical activity) enhances the efficacy of insulin therapy and reduces the chances of side effects, namely fluctuation of glucose levels, hypoglycemic episodes, and weight gain.

Human insulins (NPH and regular) remain the least expensive, especially when using premixed NPH-regular insulin 70/30. Their use should be considered when the cost of medication is a major concern for the patient. A more relaxed goal of glycemic control may be considered in order to avoid hypoglycemia when using those insulin preparations, such as a hemoglobin A_{1c} level less than 7.5% or even in the range of 7.5% to 8.5%, depending on the expected seasonal variation of hemoglobin A_{1c} (which is higher in winter[43]), individual factors, and whether the premixed insulin is used twice or three times daily.

RE-EVALUATE THE REGIMEN ROUTINELY

The insulin regimen should be re-evaluated routinely. It might need to be changed in response to the dynamic multifactorial process of progression of diabetes, change in stress level, presence or resolution of intercurrent illnesses, risk of hypoglycemia, concerns about weight gain, and cost.

Finally, adjustment of the regimen should be considered in response to improvement of glycemic control related to improvement of dietary management, exercising, weight loss, and medical therapies.

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