Progression from Basal to Pre-mixed or Rapid-acting Insulin—Options for Intensification and the Use of Pumps

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Abstract

Initiating insulin therapy is an important step in the management of patients with type 2 diabetes. The insulin regimen prescribed should be physiological and designed to control fasting and post-prandial glucose levels. The primary goals of therapy are achieving and maintaining tight glycemic control. The optimal insulin regimen should be patient-specific, taking the patient's lifestyle into consideration. As their diabetes progresses, an increasing number of patients require insulin therapy. An initial approach is to add basal insulin to oral hypoglycemic agents. When this regimen fails to achieve glycemic control, it should be intensified by either adding a rapid-acting insulin analog to control post-prandial hyperglycemia or switching to pre-mixed insulin injection initiated once daily and subsequently up to three times daily. More tools are now available, including injection devices, insulin pens, glucose monitoring devices, and insulin pumps, to overcome the barriers to initiating and intensifying insulin therapy. With new insulin analogs it is possible to intensify insulin therapy to achieve glycemic control targets without increasing the risk for hypoglycemia or causing excessive weight gain.

Keywords

Insulin therapy, basal insulin, pre-mixed insulin, insulin analogs, glycemic control

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Type 2 diabetes is a progressive disease in which beta-cell function continually declines, and most patients will eventually require insulin therapy to control hyperglycemia. In type 2 diabetes such treatment usually commences with oral antidiabetes drugs (OADs), but as beta-cell function declines, basal insulin is added to this regimen.[1] Subsequently, as diabetes progresses, this treatment often requires augmentation with bolus or prandial dosing. An increasing body of evidence suggests that early intensive glycemic control reduces long-term vascular complications and potentially may improve beta-cell function.[2,3] The importance of good glycemic control to reduce the risk for the microvascular complications of hyperglycemia is well established.[4–7]

This review considers how the use of pre-mixed (bi-phasic) insulin preparations, rapid-acting analogs, and insulin pumps as part of the intensification process can establish better glycemic control over existing therapeutic approaches, thereby minimizing vascular complications, improving quality of life, and achieving improved cost-effectiveness in treatment.

Importance of Glycemic Control in Type 2 Diabetes

Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes.[8,9] In experimental models, prolonged exposure to hyperglycemic glucose levels has been shown to result in glucotoxicity[10] and oxidative stress,[11–13] culminating in beta-cell failure. In patients with diabetes, microvascular complications include retinopathy, nephropathy, and neuropathy; macrovascular complications include heart disease, stroke, and peripheral vascular disease.[13,14] Thus, tight glycemic control is a crucial therapeutic goal in the management of type 2 diabetes. Evidence suggests that early glycemic control substantially reduces the risk for both microvascular and macrovascular events; it also delays the onset and decreases progression of these events.[4–7] Results from the UK Prospective Diabetes Study (UKPDS) showed that aggressive glycemic control using sulfonylureas or insulin in 3,867 patients newly diagnosed with type 2 diabetes significantly reduced the risk for microvascular complications compared with conventional treatment (relative risk [RR] reduction 25%; p=0.0099).[4] In this study, however, there was no significant difference in macrovascular risk among those treated

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intensively during the 10-year study period. The results of a 10-year post-study follow-up on 3,277 of the patients remaining in the trial showed that the differences between treatment groups in terms of glycemic control were eliminated during the first year, but the risk for microvascular events and for myocardial infarction and death from any cause was reduced throughout the 10 years of post-trial follow-up. This demonstrated the long-term benefit of early glycemic control in the UKPDS population.[15] The Epidemiology of Diabetes Interventions and Complications (EDIC) study originally compared intensive and conventional therapy in a population of 1,441 patients with type 1 diabetes. In the 17-year follow-up of this study, intensive treatment providing early glycemic control reduced the risk for any cardiovascular disease event by 42% (p=0.02 versus conventional treatment) and reduced the risk for non-fatal myocardial infarction, stroke, or death from cardiovascular disease by 57% (p=0.02). Microalbuminuria and albuminuria were associated with a significant increase in the risk for cardiovascular disease, but differences between treatment groups remained significant (p≤0.05). It was concluded that intensive therapy has long-term beneficial effects on the risk for cardiovascular disease in patients with type 1 diabetes.[7]

The level of glycemic control is gauged by fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), and glycated hemoglobin (HbA_{1c}), which reflects glycemic exposure during a period of approximately three months. PPG contributes significantly to the HbA_{1c} value, especially as values approach target levels,[16] and post-prandial glucose excursions have recently been linked to vascular damage.[17] Control of PPG is crucial to reaching the target HbA_{1c} levels of 6.5% as recommended by the American Association of Clinical Endocrinologists (AACE) and <7% as recommended by the American Diabetes Association (ADA).[18,19] Therefore, treatment with basal insulin alone may be insufficient to achieve glycemic control targets, and an intensified insulin regimen is often required to achieve target HbA_{1c} levels as the disease progresses.

Rationale for Early Initiation of Insulin Therapy

The Diabetes Prevention Program demonstrated that an intensive lifestyle intervention was most effective at reducing progression to diabetes in high-risk individuals, followed by metformin therapy.[20] Similarly, early intervention with insulin may potentially protect beta-cell function.[21,22] A recent randomized, parallel-group study of 382 patients with newly diagnosed type 2 diabetes looked at the effects of intensive, short-term insulin therapy on beta-cell function.[23] Patients were randomly assigned to treatment with continuous subcutaneous insulin therapy, multiple daily injections (MDIs), or oral hypoglycemic agents. Once patients had achieved and sustained on-therapy normoglycemia for two weeks, pharmacological treatment was stopped. Normoglycemia was attained by >95% of patients in the insulin treatment groups compared with 84% of those receiving oral agents. Glycemic control, in terms of fasting blood glucose, was reached significantly faster with insulin, and at one year after treatment 51% of those who had received continuous insulin and 45% of those who had received MDIs remained normoglycemic compared with 27% of patients treated with oral hypoglycemic agents. Beta-cell function was measured at the end of therapy and after one year using homeostasis model assessment of basal beta-cell function (HOMA B) and acute insulin response. Patients treated with continuous insulin therapy had an increase in HOMA B of 160% compared with 105% for those treated with oral agents. The results of this study suggest that early insulin supplementation may protect, and possibly restore, beta-cell function, and therefore alter the progressive course of diabetes.[21]

Initiating Insulin Therapy

Insulin is clearly the most effective way to control hyperglycemia. There is recent evidence to suggest that healthcare providers generally wait to initiate insulin therapy and that the HbA_{1c} value at which they will start aggressive glucose-lowering action is 9% or higher.[23,24] This reluctance may be due, in part, to concern about hypoglycemia and patient willingness and/or ability to inject insulin. A variety of insulin analogs are now available that lower the risk for hypoglycemia and limit weight gain. New insulin analogs more closely mimic the kinetic profile of endogenous insulin compared with the older human insulins. Both human insulin and insulin analogs are now available in convenient pen devices that allow more flexible dosing.[25] Pens can provide more accurate dosing compared with a vial/syringe, as well as providing more discreet dosing. They can also be easier to use/learn/teach.[26–28]

In the past, a common approach to initiating insulin therapy in type 2 diabetes was to discontinue OADs and begin with a single morning dose of basal insulin.[29] An alternative approach was subsequently developed in which a single bedtime dose of basal insulin (initially intermediate-acting neutral protamine Hagedorn [NPH] and, more recently, long-acting insulin glargine or detemir) was added to the daytime OAD regimen. The intention behind this approach is to control FPG with basal insulin and to control daytime and post-prandial hyperglycemia using OAD medications, such as sulfonylureas or other oral secretagogues that augment prandial insulin secretion. However, evidence may be lacking to substantiate the prandial benefit of sulfonylureas.[22] Alternatively, pre-mixed insulins can be an option to initiate insulin therapy. These are mixtures of insulin preparations containing fixed ratios of regular human insulin plus NPH or rapid-acting analogs plus a protaminated intermediate-acting form of a rapid-acting analog. Thus, these mixtures provide control of fasting plasma glucose and prandial plasma glucose in a single injection. Examples of pre-mixed analog preparations include a mixture containing 75% protamine-based intermediate-acting neutral protamine lispro (NPL) and 25% rapid-acting insulin lispro, and another example contains 70% insulin aspart protamine suspension and 30% insulin aspart.[30] Pre-mixed analogs have been studied to initiate insulin once or twice daily.[31]

Insulins with different pharmacodynamic profiles are available, allowing for three possible strategies in the initiation of insulin therapy: basal insulin, basal–bolus insulin (basal–bolus insulin can be used to initiate therapy for patients with HbA_{1c} levels >8.5%[32]), or pre-mixed insulin. For more detail, see *Table 1* in the online version of this article at www.touchendocrinology.com. Typically, the first strategy to consider is the addition of a basal insulin to an OAD regimen. Compared with NPH insulin, both detemir and glargine have demonstrated comparable efficacy for glycemic control, once-daily dosing, and less hypoglycemia.[33,34] In addition, the new AACE guidelines recommend the use of insulin analogs over human insulin formulations.[35]

The AACE recommends that treatment-naïve individuals whose initial HbA_{1c} value is >10% be started on insulin therapy.[19] A major challenge for primary care physicians when initiating insulin therapy is choosing when to use each of the many insulins available today; these are

rapid-acting, short-acting, intermediate-acting, long-acting, and pre-mixed insulins. To use insulin therapy most effectively, the regimen must be matched to the individual patient, considering his or her lifestyle needs and physical and mental capabilities, in addition to matching the body's physiological requirements.

Several studies have compared insulin detemir with either insulin glargine or NPH.[36–40] In a 26-week randomized, parallel-group trial including 476 patients with type 2 diabetes, addition of twice-daily insulin detemir to oral therapy achieved a decrease in HbA_{1c} of 1.8% compared with a decrease in 1.9% with NPH.[36] In both treatment groups, 70% of participants achieved a corrected HbA_{1c} ≤7.0%. In addition, there was a trend in which the proportion achieving this without hypoglycemia became higher with insulin detemir than with NPH insulin (34 versus 25%; p=0.052 [figures corrected]). Overall, compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% (p<0.001) and nocturnal hypoglycemia by 55% (p<0.001). At the end of the study, patients in the insulin detemir group had gained 1.6kg less weight and had 47% lower risk for hypoglycemia. Treatment for 52 weeks with insulin glargine added to oral therapy showed a similar reduction in HbA_{1c} levels to that achieved with NPH (-0.8 versus -0.7%), with lower rates of symptomatic hypoglycemia (33 versus 51%; p=-0.027).[40]

The findings associated with insulin detemir were confirmed in the open-label, prospective, observational Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) study (n=5,604), which enrolled 293 patients with type 2 diabetes who were switched to insulin detemir after treatment with NPH insulin or glargine in addition to oral agents.[41–44] Oral regimens remained the same and the number of daily injections did not change. Regardless of previous basal insulin regimen, patients achieved better glycemic control with insulin detemir, as shown by HbA_{1c} decreasing by 0.2% (p<0.05) among patients previously receiving NPH and by 0.6% (p<0.0001) for those who had originally received glargine. The incidence of hypoglycemia was also significantly reduced (p<0.0001). In addition, FPG decreased by 1.4mmol/l in both the NPH and glargine groups (p<0.0001). This improvement was accompanied by a weight decrease of 0.7kg (p<0.01) in those previously treated with NPH and 0.5kg (p<0.05) in patients who switched from glargine. The incidence of hypoglycemia was also reduced significantly (p<0.0001). These data provide important proof of principle that glycemic control can be improved with modern insulin analog therapy without excessive weight gain and hypoglycemia.[41]

A subgroup analysis of the German cohort from the PREDICTIVE study assessed patients over a three-month period who started on OADs only (n=1,321), NPH insulin ± OADs (n=251), or insulin glargine ± OADs (n=260) and were transferred to insulin detemir with OADs.[44] After three months of insulin detemir, hypoglycemic events/patient were reduced by 84, 80, and 90%, respectively, and no major hypoglycemic events were reported. HbA_{1c} and FBG were significantly reduced from baseline in each of the subgroups (p<0.0001 for both). These data were said to confirm the short-term safety and efficacy of insulin detemir ± OADs in a real-world scenario.

These studies showed that the modern insulin therapies detemir and glargine showed improved efficacy over NPH with decreased variability and hypoglycemic events without causing excessive weight gain.

Intensification of Basal Insulin by Adding Bolus Insulin

Basal–bolus therapy with MDIs or an insulin pump is the most physiological approach to insulin therapy. When basal insulin alone in combination with an OAD fails to control hyperglycemia, addition of prandial insulin is required. Most patients will ultimately require prandial insulin in addition to basal insulin as beta-cell function declines. Basal–bolus therapy using a rapid-acting insulin analog at mealtimes in addition to a basal insulin analog is highly effective and allows flexibility in both the timing and amount of prandial insulin dosing. Glycemic control can be improved with insulin analog therapy without excessive weight gain and hypoglycemia. Some patients may get by with the addition of prandial insulin only before the largest meal of the day, while others will require intensive basal–bolus therapy with prandial insulin before each meal. A potential concern for some patients is the need for multiple injections.

A common pitfall with basal insulin is increasing the dose too much before adding prandial insulin. This does not match the physiological needs, and predisposes the patient to fasting hypoglycemia without reaching the target HbA_{1c} level. A rule of thumb is that a patient should not be advanced to more than 0.5 units/kg bodyweight for basal insulin without first considering the addition of a rapid-acting insulin (e.g. 0.1 units/kg) with meals.[45] Insulins available for prandial coverage include regular insulin and the rapid-acting insulin analogs. The rapid-acting analogs, including aspart, lispro, and glulisine, allow closer approximation of physiological insulin secretion and also allow for flexible dosing/dosing closer to meal times.[46,47]

A series of large studies have investigated the addition of bolus insulin dosing to basal insulin while taking OADs over periods of six months to one year in populations of 271–505 patients with type 2 diabetes who, prior to the study, had received a variety of diabetes treatments.[38,48–51] In some of these trials insulin detemir was compared with either insulin glargine or NPH insulin as the basal dose with insulin aspart or human soluble insulin as the bolus treatment with concomitant oral agents such as biguanides (metformin), sulfonylureas (glimepramide), thiazolidinediones (rosiglitazone), or acarbose. In each case HbA_{1c} levels were improved by the use of bolus treatment, but the different basal treatments tended to produce non-significantly different outcomes for this parameter. An example was a trial by Hollander et al.[48] in which 319 patients with type 2 diabetes were randomized to either long-acting insulin detemir or glargine as basal therapy and insulin aspart given as a bolus dose at meal times (prandial). The bolus dose decreased HbA_{1c} levels, but after 52 weeks of treatment there was no marked difference between the two basal treatments (HbA_{1c} 7.19 and 7.03% for detemir and glargine, respectively, mean difference 0.17%, 95% confidence interval [CI] -0.07–0.40).

In another study on 387 patients with type 2 diabetes treated for 26 weeks with insulin detemir or insulin glargine as the basal treatment with insulin aspart as the bolus before meals and OADs, changes in HbA_{1c} from baseline were significantly different in both groups (-1.1 and 1.3%, respectively; p<0.0001).[50] In a study conducted by Haak et al.,[37] a population of 505 patients with type 2 diabetes was randomized to either long-acting insulin or NPH insulin as the basal dose with OADs, and both groups were given a bolus of insulin aspart. After 26 weeks of treatment there was no significant difference in FPG levels between the groups (p=0.66), but levels of HbA_{1c} were significantly reduced in both groups

(p=0.004 and 0.0001, respectively). A large trial included 393 patients with type 2 diabetes treated with insulin glargine and OADs and a single bolus dose of insulin glulisine.[51] HbA_{1c} levels showed significant reductions, which were similar whether the bolus dose was given at breakfast time or at the time of the largest daily meal.

Factors that contribute to poor glycemic control include unpredictable food intake (including conditions such as diabetic gastroparesis) and physical activity, imprecise administration of insulin by injection, and frequent illness. Continuous subcutaneous insulin infusion (CSII) provides the flexibility to control pre-meal hyperglycemia using different basal rates and post-prandial hyperglycemia by using more precise pre-meal insulin boluses. Insulin pumps allow patients to vary their basal rate on an hourly basis, decreasing the rate overnight or with exercise, or increasing it to account for insulin resistance caused by early morning secretion of cortisol and growth hormone. In type 1 diabetes, this results in lower HbA_{1c} and lower daily insulin dose than MDIs, but may cause weight gain.[51] With MDIs the peak effect of insulin may not correspond with food intake, which can lead to hypoglycemia. Insulin dosing with the pump can be calculated according to caloric and carbohydrate intake, with basal insulin adjusted to changes in activity. When there is an elevation in blood sugar, a small supplemental bolus can be delivered without concern regarding the peak effect of insulin or the need for an additional injection. This factor can moderate the extreme fluctuations in blood sugar and result in enhanced glycemic control, as evidenced by lower HbA_{1c} levels.[52] CSII by a pump is the standard of care for type 1 diabetes patients and is also used by many patients with type 2 diabetes. However, there is limited information available regarding the use of this approach to therapy in type 2 diabetes. Pump therapy is very effective, but not more effective than MDI in decreasing HbA_{1c} levels in patients with type 2 diabetes. Some small, open-label, uncontrolled studies report better quality of life in patients on pump therapy compared with those using MDI.[53] Limitations of pump therapy include the cost and a risk of mechanical failure, resulting in hypo- or hyperglycemia. Insulin pump use also requires a high degree of motivation on the part of the patient. Continuous glucose monitoring (CGM) devices are now available to better detect patterns in blood glucose variation, and are commonly used by patients using an insulin pump.

Intensification from Basal Insulin to Pre-mixed Insulin

Pre-mixed insulin preparations provide an alternative to basal–bolus dosing that does not involve multiple insulin preparations. Compared with pre-mixed human insulin, pre-mixed analogs may provide a glucose-lowering profile that more closely mimics the physiological secretion of insulin, thus providing better glycemic control and less hypoglycemia.[54] In addition, compared with pre-mixed human insulin preparations, pre-mixed insulin analogs allow patients more flexibility in timing their meals, since pre-mixed insulin analogs can be administered up to 15 minutes after starting to eat a meal.[55] Pre-mixed insulins are generally appropriate for patients who desire a convenient and simple insulin regimen, are unwilling to administer MDIs or use an insulin pump, are unwilling to or cannot undertake carbohydrate counting, have a relatively predictable (routine) lifestyle, and consume meals with approximately the same composition of calories, carbohydrates, fats, and fiber at fairly consistent and reproducible times every day.

In some patients whose hyperglycemia is not adequately controlled with oral agents and basal insulin, intensifying with pre-mixed insulin to provide basal and prandial insulin can be as effective as basal insulin plus metformin.[56] This was shown in the IMPROVE observational study in which a subgroup of 497 patients who had previously received NPH (n=497) or analog basal insulin (n=245) switched to pre-mixed insulin aspart 70/30 (BIAsp 70/30).[57] The incidence of major and minor hypoglycemia decreased from baseline to final visit (major: 0.171 to 0.011; minor: 9.70 to 5.89 events/patient-year). In addition, HbA_{1c} and fasting blood glucose were significantly reduced from baseline, as was post-prandial blood glucose, with 33.8% of patients achieving the HbA_{1c} target of <7% without hypoglycemia. In this study, bodyweight was unaffected by BIAsp 70/30 treatment. It was concluded that patients with type 2 diabetes that is inadequately controlled on basal insulins may improve their glycemic control by intensification to BIAsp 70/30 therapy. The 1-2-3 study evaluated the efficacy and safety of BIAsp 70/30 administered once, twice, or three times daily in patients with type 2 diabetes.[58] In this 48-week observational study, 41% of patients achieved target HbA_{1c} values of <7% with once-daily dosing, 70% with twice-daily dosing, and 77% with thrice-daily dosing. Therefore, a pre-mixed insulin analog is a reasonable approach for diabetes management, particularly in those individuals who tend to eat two large meals a day.

By contrast, results from the PREFER study showed that basal–bolus insulin therapy (insulin detemir plus insulin aspart) and BIAsp 70/30 were equally effective in lowering HbA_{1c} values for insulin-naïve patients (mean decrease over 26 weeks 1.69% with basal–bolus and 1.42% with pre-mixed insulin aspart 70/30; p=0.106).[59] However, basal–bolus therapy was superior for patients with prior insulin use (mean decrease 1.21% with basal–bolus and 0.75% with pre-mixed insulin aspart 70/30; p=0.0129). Rates of minor hypoglycemia were similar in both treatment groups. Major hypoglycemic episodes occurred in five patients in the basal–bolus group compared with none in the group receiving pre-mixed insulin.[59]

An open-label study compared two insulin analog therapies (prandial pre-mixed therapy [PPT] -50% insulin lispro protamine suspension and 50% insulin lispro versus insulin glargine and insulin lispro basal/bolus therapy [BBT]) in 187 type 2 diabetes patients who were previously treated with insulin glargine (≥30 units/day) plus oral agents.[60] After 24 weeks of treatment, the proportions of patients achieving target HbA_{1c} <7.0% (PPT versus BBT) were 54 versus 69% (p=0.009). PPT, however, was not shown to be inferior to BBT on the pre-specified non-inferiority margin of 0.3%. The incidence of hypoglycemic episodes was similar in the two groups. It was concluded that the reduction in HbA_{1c}, proportion of patients reaching HbA_{1c} targets, hypoglycemia, and number of required injections should be considered when deciding whether to use either PPT or BBT as insulin replacements in type 2 diabetes.

Cost-effectiveness of Intensive Insulin Therapies

The aim of early initiation of insulin therapy is to prevent short-term complications, reduce long-term morbidity and mortality, and potentially alter the natural course of type 2 diabetes. Fewer complications, including hospital visits, translates to a potential decrease in the cost of healthcare. Although optimal disease management is patient-specific, achieving and maintaining tight glycemic control are the primary goals of therapy. Because many type 2 diabetes patients will eventually require insulin

therapy, overcoming fears and therapeutic barriers to initiating therapy as early as needed is essential for reducing the vascular comorbidities of this highly prevalent disease in patients of all ages.

In an analysis of data from the PREDICTIVE study, long-term health economic outcomes associated with insulin aspart versus human soluble insulin in type 2 diabetes patients on basal–bolus therapy in Sweden, Spain, Italy, and Poland were determined.[61] The findings showed that insulin aspart was superior to human soluble insulin in both Sweden and Spain and would be considered cost-effective in Italy, with an incremental cost-effectiveness ratio of €18,597 per quality-adjusted life-year (QALY) gained, but would not be considered cost-effective in Poland. A further study aimed to evaluate the long-term clinical and economic outcomes derived from insulin detemir and NPH insulin in combination with mealtime insulin aspart in patients with type 1 diabetes at centers in Belgium, France, Germany, Italy, and Spain.[62] Insulin detemir produced cost savings in Belgium, Germany, and Spain. In France and Italy, lifetime costs were slightly greater with the detemir arm, and incremental cost-effectiveness ratios were €519 per QALY gained and €3,256 per QALY gained, respectively. Insulin detemir was therefore considered more likely to be used as a treatment strategy than NPH in Belgium, Germany, and Spain, but is highly cost-effective in France and Italy in patients with type 1 diabetes.

The INITIATE clinical trial demonstrated improvements in HbA_{1c} with BIAsp 70/30 versus glargine in patients poorly controlled on OAD therapy.[55] Data from this study were projected over 35 years to account for the effects on life expectancy (LE), quality-adjusted life expectancy (QALE), cumulative incidence of diabetes-related complications, and direct medical costs (based on 2004 costs in US$). Results showed that the improvements in glycemic control were projected to lead to gains in LE (0.19±0.24 years) and QALE (0.19±0.17 years) favoring BIAsp 70/30 versus glargine. Treatment with BIAsp 70/30 was also associated with reductions in the cumulative incidence of diabetes-related complications, notably in renal and retinal conditions. The incremental cost-effectiveness ratio was $46,533 per QALY gained with pre-mixed insulin aspart 70/30 versus glargine (for patients with baseline HbA_{1c} ≥8.5%, it was $34,916). Total lifetime costs were compared with efficacy rates in both arms as a ratio, which revealed that the lifetime cost per patient treated successfully to target HbA_{1c} levels of <7.0% and ≤6.5% were $80,523 and $93,242 lower with BIAsp 70/30 than with glargine, respectively. Thus long-term treatment with BIAsp 70/30 was projected to be cost-effective for patients with type 2 diabetes insufficiently controlled on OAD therapy alone compared with glargine.[63]

Conclusion

A number of new clinical tools are available for the treatment of type 2 diabetes, including basal, prandial, and pre-mixed insulin analogs and new insulin delivery devices. There is no denying that legitimate concerns regarding insulin use exist, but insulin is often necessary to reach blood glucose goals. Healthcare providers can reduce the perceived negative aspects of insulin by addressing patient concerns and barriers and providing information to support insulin use and improve metabolic control. As diabetes progresses, decreasing glycemic control necessitates treatment intensification. Options for this initially include the addition of basal insulin to OADs; this often uses long-acting insulins to provide a more consistent efficacy. Alternatively, an automated pump dosing system can be used to provide a constant delivery. Basal dosing regimens can be intensified with the addition of prandial bolus insulin doses, a strategy that has been shown to markedly reduce HbA_{1c} levels. Another alternative to multiple injected insulin doses is to use a pre-mixed preparation. Various pre-mixed insulin analogs are commercially available and provide simultaneous coverage of fasting and prandial glucose. The availability of multiple treatment regimens and insulin types allows for treatment to be tailored to specific patient needs. Studies using both pre-mixed and basal–bolus regimens have demonstrated that intensification improves quality of life, decreases complications, and slightly increases LE. Analysis of these criteria has shown that such approaches are cost-effective. Treatment intensification should therefore be considered for all patients with progressing diabetes to both decrease the worsening disease burden and reduce the high long-term costs of treatment and care. ■

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