Options for Intensification with Biphasic Insulins in Patients with Type 2 Diabetes Not Achieving Glycemic Control

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Citation

Abstract

Background: In type 2 diabetes, simple, convenient and effective regimens should encourage timely insulin initiation and improve outcomes. Long- and rapid-acting insulin analogues more closely mimic endogenous basal/prandial insulin secretion than human equivalents. Premixed insulin analogues deliver prandial and basal insulin in one formulation and can be administered 1-3 times daily. Premixed insulin may, therefore, provide an alternative to basal–bolus regimens for intensification of insulin therapy.

Objectives: The aim of this commentary was to show how biphasic insulin therapy may offer a simple and effective intensification option for patients with type 2 diabetes who do not achieve adequate control with existing insulin therapies.

Methods: A literature search using the PubMed database (years: January 1997- September 2010) was carried out using the search terms diabetes AND ((biphasic OR bi-phasic) AND (insulin OR insulins)) OR ((premix OR pre-mix) AND (insulin OR insulins)). Clinical trials, systematic reviews, case reports or clinical practice guidelines that addressed topics of interest with regard to premixed insulin analogues/analogue regimens and intensification strategies were identified and included.

Results: Clinical data show that premixed insulin analogues reduce hemoglobin A1C and fasting plasma glucose to a similar extent as premixed human insulin, but have advantages in terms of postprandial glucose control, incidence of hypoglycemia, and convenience. Premixed insulins may also provide benefits to glycemic control (reduced HbA1c, fasting and postprandial plasma glucose) in patients failing to achieve targets on basal insulin. In addition, premixed insulin analogue regimens generally compare well with basal–bolus regimens. Conclusions: Premixed insulin analogues offer a simple intensification option in patients with type 2 diabetes not achieving adequate control with existing insulin therapy. Premixed insulin analogues may offer a viable alternative to basal–bolus regimens and an improved physiologic profile compared with human equivalents.

INTRODUCTION

The benefits of glycemic control with respect to prevention of microvascular and neuropathic complications have been established for many patients with both type 1 and type 2 diabetes. All patients with diabetes should therefore be encouraged to achieve glycemic levels as near to normal as possible without inducing clinically significant hypoglycemia.

Because type 1 diabetes is characterized by an absolute deficiency in insulin secretion, all patients with this condition require insulin therapy. In contrast, patients with type 2 diabetes may initially be treated with lifestyle changes, either alone or in combination with oral antidiabetic agents. However, because pancreatic β cell function progressively declines in type 2 diabetes, most patients will eventually require insulin therapy. This inevitability was clearly shown in the ADOPT (A Diabetes Outcome Progression Trial) study, which evaluated the use of oral antidiabetic agents in patients with recently diagnosed type 2 diabetes. This study demonstrated that failure to maintain glycated hemoglobin (A1C) below 7% occurred after 33 months with glyburide (a sulfonylurea), 45 months with metformin, and 57 months with rosiglitazone (a thiazolidinedione).

The goal of insulin therapy is to mimic normal physiologic secretion of insulin as closely as possible in order to control both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Increasing emphasis has been placed on the contribution of PPG to the overall glycemic burden, with evidence suggesting that PPG contributes as much as, or
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even more than, FPG to overall glycemic burden as A1C values approach 7%. In addition to its impact on glycemic burden, PPG has been implicated in the development of both micro- and macrovascular complications of diabetes. 

Despite the proven importance of achieving good glycemic control, >40% of adults diagnosed with type 2 diabetes are not achieving their glycemic goals. Both healthcare providers and patients may be reluctant to start insulin therapy, as illustrated in the Diabetes Attitudes Wishes and Needs (DAWN) study. This study revealed that many patients see insulin initiation as a “failure” on their part, while healthcare providers will often delay insulin until deemed “absolutely necessary.” Many patients also reported that their insulin regimen was too complicated and more than one-third reported frustration with medication-taking.

The use of insulin regimens that are more simple or convenient may therefore have an important role in reducing barriers to insulin therapy and improving patient outcomes through increased adherence. The most physiologic insulin regimens involve basal–bolus combinations of the recently developed insulin analogues. The long-acting analogues glargine and detemir more closely mimic basal insulin production than human insulin, while the rapid-acting analogues, aspart, lispro and glulisine, mirror the postprandial (bolus) release of endogenous insulin following a meal. However, insulin-naïve patients with type 2 diabetes may prefer to begin insulin therapy with a simpler approach than basal–bolus therapy. Instead, clinicians often start with less intensive regimens and then adjust as needed. Patients with type 2 diabetes usually start insulin therapy with either basal insulin alone or basal with prandial insulin at 1 or 2 meals.

In contrast, biphasic insulin regimens use a single insulin preparation to deliver prandial and basal insulin requirements. Premixed insulin analogues are derived from rapid-acting insulin analogues and consist of a mixture of rapid-acting insulin analogue and its intermediate-acting protaminated form. Protamination is a process that produces an analogue with an intermediate duration of action. Biphasic insulins are typically administered once, twice, or thrice daily.

Although insulin intensification strategies (i.e. moving to basal insulin plus a single short-acting insulin injection or to premixed insulin preparations) are successful for many patients, some may experience hypoglycemia and weight gain with intensive insulin therapy. The 4-T (Treat-To-Target in Type 2 diabetes) open-label trial randomized patients with suboptimal glycemic control while receiving maximally tolerated doses of metformin and sulfonylurea to 3 treatment regimens: once- or twice-daily basal insulin detemir, twice-daily biphasic insulin aspart 30, or thrice-daily prandial insulin aspart. The 1-year results demonstrated that all 3 add-on regimens significantly improved glycemic control. However, hypoglycemia was more frequent, and mean weight gain was considerably greater, with biphasic/premixed and prandial regimens than with basal insulin. Another randomized, open-label trial showed that both prandial premixed therapy and basal-bolus therapy (in combination with oral agents) effectively lowered A1C levels to <7% in patients with type 2 diabetes who had previously been treated with insulin glargine plus oral agents; hypoglycemia rates and weight gain were similar in the two groups.

The availability of different insulins and of various insulin delivery methods allows insulin regimens to be individualized to meet a patient’s particular needs and lifestyles. This commentary aims to show how biphasic insulin therapy may offer a simple and effective intensification option for patients with type 2 diabetes who do not achieve adequate control with existing insulin therapies.

METHODS

This review is based on a literature search of the PubMed database (from 1 January 1997 to 30 September 2010) using the following search strategy: (diabetes type 2 OR diabetes type II OR T2DM) AND ([(biphasic OR bi-phasic) AND (insulin OR insulins)] OR [(premix OR pre-mix) AND (insulin OR insulins)]). The following limits were applied to the search strategy: English language, adult patients (≥19 years), clinical trials (of any design), systematic reviews, practice guidelines, case reports. Identified articles (N=86) were included if they addressed the following topics: 1) comparison of the efficacy and safety of biphasic insulin analogues with that of biphasic human insulin; 2) efficacy and safety of biphasic insulin analogue regimens when used to intensify insulin therapy in patients inadequately controlled on less intensive insulin therapy; 3) comparison of the efficacy and safety of biphasic insulin analogue regimens with that of other intensification strategies; or 4) comparison of the efficacy and safety of biphasic insulin aspart with that of biphasic insulin lispro. Additional articles
addressing these topics were also identified from the reference lists of the articles identified by the initial literature search. The intensification sub-section of the Results section focuses on data from randomized trials.

RESULTS

BIPHASIC INSULIN ANALOGUES

COMPARISON WITH BIPHASIC HUMAN INSULIN

Premixed insulin analogues reduce A1C and FPG to a similar extent as premixed human insulin, but provide improved control of PPG. For example, a systematic review of 16 studies that compared premixed insulin analogues with premixed human insulin showed that pooled treatment differences for FPG (0.2 mmol/L [95% CI: –0.1; 0.6 mmol/L]) and A1C (–0.05% [95% CI: –0.14; 0.04%]) were not statistically significant. Premixed insulin analogues were, however, more effective than premixed human insulin in reducing PPG (mean treatment difference, –1.1 mmol/L [95% CI: –1.4; –0.7]). Compared with premixed human insulin, PPG reductions of 5.4–30.6 mg/dL have been reported for biphasic insulin aspart 70/30 or insulin lispro mix 75/25 in clinical trials. In a 48-week, randomized, open-label trial, 437 patients with type 2 diabetes were randomized (3:1) to receive insulin aspart 70/30 twice daily immediately before meals or premixed human insulin twice daily 30 minutes before meals. After 24 weeks, the mean post-breakfast PPG was 29% lower with biphasic insulin aspart 70/30 twice daily than with premixed human insulin 70/30 twice daily (73.8 ± 2.9 vs. 103.3 ± 5.0 mg/dL; P < 0.001).

Premixed insulin analogues also have a faster onset of action (30–40%) than equivalent human insulin preparations, and thus can be administered closer to mealtime. In a small, open-label, single-center, randomized, four-period crossover study in 31 patients (mean age 57 years; mean duration of diabetes 12 years; mean baseline A1C 8.7%) with type 2 diabetes who had been receiving insulin for at least 6 months, biphasic insulin aspart 30/70 injected immediately before a meal was associated with significantly lower serum glucose AUC\(_{0-4h}\), compared with premixed human insulin preparations administered 15 minutes before or immediately before eating (P = 0.0057 and P = 0.0006, respectively). C\(_{\text{max}}\) was also significantly lower with biphasic insulin aspart 30/70 immediately before eating (13.8 ± 2.8 mmol/L) than with premixed human insulin immediately before eating (14.9 ± 4.2 mmol/L; P = 0.007).

An open-label, multinational, non-randomized, 26-week observational study, in 3856 patients (mean age 57 years; mean duration of diabetes 10.7 years; mean baseline A1C 9.21%) with type 2 diabetes previously receiving human premixed insulin with or without oral antidiabetic drugs showed that switching patients from biphasic human insulin 70/30 to biphasic insulin aspart 70/30 resulted in significant improvements in glycemic control; after 6 months, all glycemic parameters were significantly improved, with mean overall reductions from baseline of 20%, 34% and 33% for A1C, FPG and PPG, respectively (all P<0.0001). The mean absolute reduction in A1C from baseline after 6 months was 1.84% with biphasic insulin aspart 70/30 and the percentage of patients achieving A1C <7% increased from 6.3% to 40.5%. In addition, there was a reduced risk of major (–0.33 events/patient–year), minor (–5.70 events/patient–year) and nocturnal (2.17 events/patient–year) hypoglycemic events (all P < 0.0001).

Glycemic control using twice-daily biphasic insulin aspart 30 was also examined in a subset of patients from the PRESENT study (Physicians' Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy). This subset was composed of 1989 Chinese patients (mean age 52.8 years; mean duration of diabetes 6 years; mean baseline A1C 9.65%) with uncontrolled type 2 diabetes treated with human insulins. Patients had improvements in glycemic control when their treatments were switched from human insulin to biphasic insulin aspart. Reductions in A1C ranging from 1.17% to 2.43%, improvements of FPG ranging from 1.93 to 3.86 mmol/L, and PPG ranging from 3.47 to 6.13 mmol/L were achieved across the subgroups after the 3-month therapy.

The premixed insulin analogues, biphasic insulin aspart 70/30 and insulin lispro mix 75/25, are available in prefilled pen devices, which are easy to use and do not require refrigeration once opened. These devices have also been shown to be associated with improved health-economic and quality-of-life outcomes versus the vial and syringe. In a retrospective, longitudinal, intra-patient analysis of 486 adults with type 2 diabetes (mean age 45.1 years) who switched from an insulin analogue vial and syringe (n = 233) or a human insulin vial and syringe (n = 253) to a biphasic insulin analogue pen device, the medication possession ratio (a measure of adherence) increased from 59% to 68% (p<0.01). In addition, significant decreases in hypoglycemia-attributable emergency department visits (OR
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0.36 [95% CI 0.16; 0.84; P < 0.05) and physician visits (OR 0.39 [95% CI 0.20–0.77]; p<0.05) were recorded. This led to a reduction in total mean all-cause annual treatment costs of $1748/patient (P < 0.01), including reduced hypoglycemia-attributable costs ($908/patient; P < 0.01) and other diabetes-attributable costs ($643/patient; P < 0.01). A summary of available biphasic formulations is given in Table I.

Figure 1
Table I. Insulin premixed formulations and presentations in the USA

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Trade name</th>
<th>Devices</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin® 70/30</td>
<td>Natron® 70/30</td>
<td>Vial, cartridge</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Humulin® 70/30</td>
<td>Natron® 70/30</td>
<td>Pen, prefilled vial</td>
<td>Eli Lilly</td>
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<tr>
<td>Humulin® 50/50</td>
<td>Natron® 50/50</td>
<td>Vial, cartridge</td>
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<td>Humulin® 50/50</td>
<td>Natron® 50/50</td>
<td>Pen, prefilled vial</td>
<td>Eli Lilly</td>
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**USE IN INTENSIFICATION STRATEGIES**

For patients already receiving both basal and prandial insulin, therapy can be intensified through a number of approaches, including: additional injections of a rapid-acting insulin given before meals (i.e., basal–bolus therapy); increasing the frequency of premixed insulin analogue from once daily to twice daily; increasing the frequency of premixed insulin analogue from twice daily to 3 times daily; changing from a premixed insulin analogue twice daily to intensive basal–bolus therapy (low levels of basal insulin are supplemented with larger insulin administration at mealtimes). Table II provides a summary of intensification options in patients not achieving optimal A1C on their current insulin regimen.

**CLINICAL TRIALS COMPARING INTENSIFICATION OPTIONS**

Premixed insulin analogues may offer a viable alternative to basal–bolus regimens, although both options have advantages and disadvantages. A number of studies have compared premixed insulin analogues with basal–bolus regimens. In a 26-week treat-to-target trial, 719 patients with
type 2 diabetes uncontrolled by oral antidiabetic agents with or without basal insulin were randomized 3:1 to receive analogue basal–bolus therapy (insulin detemir once daily and insulin aspart at meal times) or biphasic insulin aspart 70/30 twice daily. Baseline characteristics were similar for the two treatment groups (mean age 60.3 years and 61.7 years; mean duration of diabetes 9.4 years and 8.9 years; mean baseline A1C 8.52% and 8.4% for the basal-bolus and biphasic insulin aspart groups, respectively). Baseline A1C was reduced by 1.56 (to 6.96%) with basal–bolus treatment and by 1.23 (to 7.17%) with biphasic insulin aspart (P = 0.0052 in favor of basal–bolus therapy). Patients previously treated with basal insulin had greater A1C reductions with basal–bolus therapy than with biphasic insulin aspart (1.21 vs. 0.75%; P = 0.0129), whereas insulin-naive patients had similar reductions with both regimens (1.69 vs. 1.42%; P = 0.106). Overall, major hypoglycemia occurred in 5 basal–bolus patients (0.9%) and in no patients with biphasic insulin aspart 70/30.

In a randomized, open-label parallel-group trial in 394 patients with type 2 diabetes previously receiving insulin once or twice daily, biphasic insulin aspart given 3 times daily (30/70 or 50/50, depending on body mass index [BMI], at breakfast and lunch plus 70/30 at dinnertime) was as efficacious as a basal–bolus insulin regimen of NPH plus 4-times-daily insulin aspart. Baseline characteristics were similar for the two treatment groups (mean age 59.5 years and 59.8 years; mean duration of diabetes 14.2 years and 12.8 years; mean baseline A1C 9.1% and 9.1% for the biphasic insulin aspart and basal-bolus groups, respectively). After 16 weeks, mean A1C decreased from 9.1± 0.7% to 7.8 ± 1.0% with both treatments (treatment difference, –0.05% [95% CI –0.24; 0.14]). In addition, no significant difference in mean plasma glucose profile was observed (treatment difference 0.23 mmol/L [95% CI 0.15; 0.61]), and hypoglycemic events were similar between the 2 groups (major events: 0.1 vs. 0 events/patient–year; minor events: 7.4 vs. 7.1 events/patient–year, respectively).

The 3-year 4-T open-label trial randomized 708 patients who had suboptimal glycemic control on maximally tolerated doses of metformin and sulfonylurea to three treatment regimens: once or twice-daily basal insulin detemir, twice-daily biphasic insulin aspart 30, or thrice-daily prandial insulin. Each treatment group had a specific glucose testing schedule and a computerized algorithm for adjusting the dose, based on the results of those tests. In the basal insulin group, detemir was given only in the evening, unless high glucose values persisted in the late afternoon; in such cases, a second daily injection was added each morning. The primary endpoint was the A1C level at 1-year treatment, after which a 2-year phase of further intensification of treatment for each treatment group followed. In this second phase of the study, sulfonylurea therapy was replaced by a second type of insulin if glycated hemoglobin levels of >6.5% were not achieved with a single type of insulin. The 1-year results demonstrated that all three regimens, when added to metformin and sulfonylurea therapy, significantly improved glycemic control. The proportions of patients with a glycated hemoglobin level >6.5% were 17.0%, 23.9%, and 8.1% in the biphasic/premixed, prandial, and basal group, respectively; mean glycated hemoglobin levels were similar in the biphasic/premixed (7.3%) and the prandial groups (7.2%) (P = 0.08), but higher in the basal group (7.6%, P<0.001 for both comparisons). However, hypoglycemia was more frequent, and the mean weight gain was considerably greater, with premixed and prandial regimens than with basal insulin. Mean numbers of hypoglycemic events per patient per year were 5.7, 12.0, and 2.3 in the biphasic/premixed, prandial, and basal group, respectively; mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg in the biphasic/premixed, prandial, and basal group, respectively. The 3-year results showed that the median achieved glycated hemoglobin was similar in all three groups (7.1%, 6.8%, and 6.9% in the biphasic/premixed, prandial, and basal group, respectively). However, fewer patients achieved glycemic targets (6.5%) in the biphasic/premixed group than in either the prandial or the basal groups, and fewer hypoglycemic episodes and less weight gain occurred in patients in the basal group.

Another randomized, open-label trial compared two analogue insulin therapies (prandial premixed therapy vs. basal-bolus therapy) in 374 type 2 diabetic patients previously treated with insulin glargine plus oral agents. Patients received prandial premixed therapy (lispro mix 50/50: 50% insulin lispro protamine suspension and 50% lispro) thrice daily with meals, or basal-bolus therapy (glargine at bedtime plus mealtime lispro), over 24 weeks. Investigators were allowed to replace lispro mix 50/50 with lispro mix 75/25 at the evening meal if the fasting plasma glucose target was unattainable. This noninferiority trial showed that A1C was significantly reduced from baseline for both regimens (P < 0.0001). The difference in A1C change from baseline to the end point (basal-bolus therapy
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minus prandial premixed therapy) was $0.22\%$ (90% CI $0.38$ to $0.07$). Thus, noninferiority of prandial premixed therapy to basal-bolus therapy was not demonstrated based on the pre-specified noninferiority margin of $0.3\%$. Compared with the prandial premixed regimen, the basal-bolus regimen was associated with a greater reduction in A1C from baseline and a larger proportion of patients who achieved A1C targets of $<7.0$ and $<6.5\%$, but hypoglycemia rates and weight gain were similar in the 2 groups.\(^{27}\)

### COMPARISON OF DIFFERENT BIPHASIC INSULIN ANALOGUE FORMULATIONS

Limited data are available comparing the efficacy and safety of different biphasic insulin analogues, partly due to the more recent introduction of insulin lispro mix. In a randomized, open-label, crossover study in 137 patients (133 evaluable patients: mean age 62.3 years; mean duration of diabetes 12.1 years; mean baseline A1C 8.5\%) with type 2 diabetes receiving conventional insulin treatment, biphasic insulin aspart 70/30 (twice daily) and insulin lispro mix 75/25 (twice daily) provided comparable glycemic control (upper limit of 90% CI for estimated treatment difference in A1C was $< 0.4\%$). The two agents also had similar safety profiles, with 0.69 and 0.62 hypoglycemic episodes per month ($P = 0.29$).\(^{37}\) However, in a second, randomized, open-label, single-dose, crossover study in 61 insulin-treated patients (mean age 60.1 years; mean duration of diabetes 11.6 years; mean baseline A1C 8.3\%) with type 2 diabetes, PPG levels were significantly lower with biphasic insulin aspart 70/30 compared with premixed human insulin (17% lower; $P < 0.001$) and insulin lispro mix 75/25 (10% lower; $P < 0.05$).\(^{38}\)

### TITRATION APPROACHES WITH BIPHASIC INSULIN ANALOGUES

Premixed insulin analogues can be given in once-, twice- or in some cases, up to thrice-daily regimens, allowing the dose to be titrated to meet glycemic goals.

In an observational study in 100 adults (mean age 56.7 years; mean duration of diabetes; mean baseline A1C 8.6\%) with type 2 diabetes receiving oral antidiabetic agent therapy with or without basal insulin, patients discontinued prior basal insulin and added 1 injection of biphasic insulin aspart, increasing frequency to 2 or 3 times daily according to the level of glycemic control.\(^{39}\) Addition of once-daily biphasic insulin aspart 70/30 before dinner enabled 21\%  (95% CI: 13.5; 30.3) of the patients to achieve A1C $\leq 6.5\%$, and 41\% (95% CI: 31.3; 51.3) to achieve A1C $< 7\%$. With 2 daily injections of biphasic insulin aspart 70/30, these glycemic goals were achieved by 52\% and 70\% of subjects, respectively. With 3 daily injections of biphasic insulin aspart 70/30, 60\% (95% CI: 49.7; 69.7) of patients achieved A1C $\leq 6.5\%$ and 77\% (95% CI: 67.5; 84.8) achieved A1C $< 7\%$.

In a further study, the ability of biphasic insulin aspart 70/30 treatment to improve glycemic control was investigated in 150 patients (mean age 57.9 years; mean baseline A1C 8.4\%) with type 2 diabetes who had failed to achieve glycemic targets on maximum doses of oral antidiabetic agent therapy or existing insulin regimens. Patients were started on biphasic insulin aspart 70/30 once, twice, or 3 times daily depending on previous insulin therapy (naive, basal, or premixed) and A1C levels ($<8.5\%$ or $>8.5\%$).\(^{39}\) To track the impact of the regimen on blood glucose, patients initially undertook a 7-point self-monitoring of blood glucose schedule (3 pre-meal, 3 post-meal, and 1 bedtime measurement). Once titration was stabilized, patients were instructed to alternate self-monitoring using a 4-point (3 pre-meals plus bedtime) and a 3-point regimen (post-meal only). Patients were taught to self-titrte based on a predefined dosing schedule, developed from on treat-to-target research. (Table III) Patients were requested to up-titrte their dose no more than twice a week and with 3 days between changes. It was preferable for patients to only make 1 upward dose change at a time if injecting more than once daily; however, downward changes could be performed at any time. Two approaches to dose titration were taught: one for pre-meal one for post-meal. Patients were taught first to use the pre-meal algorithm; following this, they were instructed in the post-meal algorithm. After 6 months, numerical reductions in A1C of 0.8\%–1.3\% were reported. After 18 months, all patients experienced significant reductions in A1C (mean [SEM], 1.9\% [0.1\%]; $P < 0.001$), FPG (2.8 [0.2] mmol/L; $P < 0.001$) and PPG (2.9 [0.2] mmol/L; $P < 0.001$) irrespective of pre-study regimen. Overall, 91\% of patients achieved A1C $< 7\%$ and 52\% achieved A1C $\leq 6.5\%$.\(^{39}\)
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Figure 3
Table III. Dose titration schedule used with biphasic insulin aspart 70/30 injected directly before meals

MATCHING INSULIN REGIMENS TO THE PATIENT

For some elderly type 2 diabetes patients, postprandial injection of biphasic insulin aspart 70/30 may be an acceptable alternative to standard preprandial injection, especially where there is uncertainty about the quantity of food that may be eaten during a meal. In a study by Warren et al.,

32 93 elderly patients (mean age 93 years; mean duration of diabetes 17.5 years; mean baseline A1C 7.7%) with type 2 diabetes stabilized on biphasic insulin aspart 70/30 twice daily were randomized to receive their insulin dose either 5 minutes before meals or 15–20 minutes after meal onset for 4 weeks. The mean plasma glucose values during a 4-hour meal test at the end of each treatment were similar following pre- or postprandial injection (153 ± 58 mg/dL and 161 ± 59 mg/dL, respectively), although the mean increase in self-measured blood glucose values was significantly greater after postprandial injection than after preprandial injection (treatment difference: 16.3 mg/dL [95% CI 0.5, 29.3]). There was no increase in hypoglycemia in the postprandial group (113 episodes vs 125 episodes in the preprandial group).

A separate retrospective case series analysis study in 12 older patients (mean age 68.4 years; mean duration of diabetes 14.6 years; mean duration of insulin use 8.2 years) with type 2 diabetes showed that increasing the frequency of biphasic insulin aspart 70/30 from a twice-daily regimen to a 3-times-daily regimen was associated with a decrease in mean A1C from 8.4% to 7.2%, with only 1 patient remaining >8%. Furthermore, no patients reported major or minor hypoglycemic episodes, an important consideration as this population is more susceptible to hypoglycemia.

In patients receiving biphasic insulin, dietary counseling may help to improve outcomes. A 24-week trial in 4875 insulin-naïve patients (mean age 53 years; mean baseline A1C 9.9%) with poorly controlled type 2 diabetes examined glycemic control and hypoglycemia development after initiation of biphasic insulin according to one of three dietary counseling strategies (no counseling, 1 telephone session with a dietary counselor or 3 telephone sessions). Patients self-administered twice-daily biphasic insulin aspart 70/30 with 6 units before breakfast and 6 units before supper, titrating according to self-measured blood glucose values. After 24 weeks mean A1C decreased approximately 2.5% to 7.44-7.49%, and an A1C value <7% was achieved by ~41% of patients. Rates of major and minor hypoglycemia were low, but decreased with the level of dietary counseling (minor hypoglycemia: 56 vs 50 vs 45 episodes/100 patient–years with no counseling, 1 session and 3 sessions, respectively; major hypoglycemia, 9 vs 6 vs 4 episodes/100 patient-years; P <0.001 for 3 sessions vs no counseling).

DISCUSSION

The available data on intensification of insulin therapy using premixed insulin analogues are mainly derived from open-label or non-comparative studies, and interpretations must therefore be made with caution.

Overall, the current clinical evidence shows that premixed insulin analogues reduce A1C and FPG to a similar extent as premixed human insulin. However, premixed insulin analogues may offer a number of potential advantages compared with premixed human insulin.

Clinical data indicates that premixed insulin analogues offer greater glycemic control compared with human insulin preparations. In particular, premixed insulin analogues may have the potential to improve glycemic control in some patients whose current regimen has failed to achieve targets.

In addition, premixed insulin analogues have a faster onset of action than equivalent human insulin preparations, which enables administration closer to mealtimes without compromising efficacy. Indeed, for patients with type 2 diabetes, biphasic insulin aspart 30 can be administered within 15 minutes before or after meal initiation. The shorter
interval required between injection and mealtimes with premixed insulin analogues may offer greater convenience to patients, and could potentially improve adherence compared with premixed human insulin.

Using premixed insulin analogues can simplify insulin regimens with a single insulin formulation to meet both prandial and basal insulin requirements, and often fewer injections than a basal–bolus regimen. A simpler regimen may offer greater convenience to patients and increase adherence to treatment. This may be particularly important in elderly patients and those with comorbid conditions or visual or cognitive impairment. In addition, because postprandial hyperglycemia may be a more prevalent abnormality in glucose homeostasis in elderly patients, treatments that address both basal and prandial insulin requirements may be particularly appropriate in this population.

The basal components of all premixed insulins have an intermediate-acting, NPH-like profile rather than the more physiologic profile of the long-acting insulin analogues, insulin detemir and insulin glargine, which last for up to 24 hours with no pronounced peak effect. Therefore, regimens using premixed insulin analogues are best suited to patients who eat at fixed times. Individuals who do not have a regular meal schedule may find a basal–bolus regimen more convenient and effective; as such regimens can be matched to any glycemic pattern and to any diet to achieve glycemic control.

An individually tailored approach is key to successful treatment outcomes; the choice of insulin regimen needs to take into account the patient’s preferred device and injection frequency, approach to self-monitoring blood glucose, lifestyle factors, and presence of postprandial hyperglycemia, as well as individual capability and access to support.

In conclusion, premixed insulin analogues provide control of PPG with a greater degree of flexibility in dosing time and without compromising efficacy, compared with human insulins. Premixed insulin analogues may also offer a viable alternative to basal–bolus regimens and an improved physiological profile compared with human equivalents. Therefore, premixed insulin analogues may offer a simple and effective intensification option for patients with type 2 diabetes who do not achieve adequate control with existing insulin therapies.

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References
11. Bastyr EJ 3rd, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. Diabetes
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Care. 2000;23(9):1236–1241.
34. Gao Y, Guo XH. Switching from human insulin to biphasic insulin aspart 30/70 treatment gets more patients with type 2 diabetes to reach target glycosylated hemoglobin < 7%: the results from the China cohort of the PRESENT study. Chin Med J (Engl) 2010;123(9):1107–1111.

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