Efficacy and safety of biphasic insulin aspart and biphasic insulin lispro mix in patients with type 2 diabetes: A review of the literature

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ABSTRACT

Type 2 diabetes (T2D) represents an escalating burden worldwide, particularly in China and India. Compared with Caucasians, Asian people with diabetes have lower body mass index, increased visceral adiposity, and postprandial glucose (PPG)/insulin resistance. Since postprandial hyperglycemia contributes significantly to total glycemic burden and is associated with heightened cardiovascular risk, targeting PPG early in T2D is paramount. Premixed insulin regimens are widely used in Asia due to their convenience and effectiveness. Data from randomized controlled trials and observational studies comparing efficacy and safety of biphasic insulin aspart 30 (BIAsp 30) with biphasic insulin lispro mix (LM 25/50) and versus other insulin therapies or oral antidiabetic drugs (OADs) in T2D demonstrated that BIAsp 30 and LM 25/50 were associated with similar or greater improvements in glycemic control versus comparator regimens, such as basal–bolus insulin, in insulin-naïve, and prior insulin users. Studies directly comparing BIAsp 30 and LM 25 provided conflicting glycemic control results. Safety data generally showed increased hypoglycemia and weight gain with premixed insulins versus basal–bolus insulin or OADs. However, large observational trials documented improvements in glycated hemoglobin, PPG, and hypoglycemia with BIAsp 30 in multi-ethnic patient populations. In summary, this literature review demonstrates that premixed insulin regimens are an appropriate and effective treatment choice in T2D.

Key words: Biphasic insulin aspart, biphasic insulin lispro mix, postprandial glucose, premixed insulin, type 2 diabetes

INTRODUCTION

Diabetes management guidelines focus on treatment individualization, including ethnic/cultural needs and risk of hypoglycemia and weight gain.[1] Asian patients have higher postprandial glucose (PPG) levels compared with other regional groups[2] and currently, a large proportion of Asian patients with type 2 diabetes (T2D) are treated with human premixed insulin.[3] This review examines studies of efficacy and safety involving insulin analogs, biphasic insulin aspart 30 (BIAsp 30), and biphasic insulin lispro mix (LM 25/50).

DIABETES: AN EVER-INCREASING PUBLIC HEALTH BURDEN

Globally, the number of people with diabetes continues to rise year on year, providing a major challenge to public health and an enormous economic burden.[1,4] The International Diabetes Federation estimates 382 million people globally had diabetes in 2013, with more than 160 million from China and India alone.[4] T2D accounts for approximately 90% of all cases worldwide, and a worrying
trend is the increasing diagnosis of T2D in children and adolescents.\(^\text{[8]}\)

In addition to economic development, rapid transitions to Western lifestyles, and increasing obesity rates,\(^\text{[4,6]}\) other more inherent reasons might explain the escalating burden of T2D in regions such as Asia.\(^\text{[2,7-11]}\) For example, in a study of healthy lean individuals, Asian patients had higher PPG levels and lower insulin sensitivity than Europeans in response to a 75 g carbohydrate load.\(^\text{[2]}\) A change in dietary patterns from traditional high-fiber, low-fat diets to Westernized diets (i.e., high intake of fats, carbohydrates, and trans-fatty acids) has been linked to postprandial hyperglycemia and hyperinsulinemia.\(^\text{[11]}\)

**Importance of Targeting Postprandial Glucose**

While T2D therapy is directed toward lowering glycated hemoglobin (HbA1c) levels with emphasis on fasting plasma glucose (FPG), targeting PPG excursions is also important for achieving HbA1c goals.\(^\text{[12]}\) In T2D, the contribution of PPG toward total glycemic burden is enormous at any level of glycemic control. Furthermore, PPG contribution relative to FPG is greatest when HbA1c is <7.5\%\(^\text{[13]}\). Yet many patients experience significant PPG excursions even in the context of good glycemic control according to HbA1c and FPG.\(^\text{[14,15]}\)

PPG elevations are detectable early in T2D progression.\(^\text{[12]}\) They result from loss of first-phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and diminished suppression of hepatic glucose output after meals due to insulin insufficiency.\(^\text{[12,16]}\) Since postprandial hyperglycemia is an earlier biochemical abnormality than fasting hyperglycemia,\(^\text{[13]}\) any treatment strategy addressing PPG may help to reduce the risk of complications.\(^\text{[18]}\) In the presence of insulin resistance, fasting insulin response is maintained in early T2D, while insulin response to meal-related hyperglycemia is inadequate,\(^\text{[17]}\) highlighting the importance of targeting PPG early in the disease course.\(^\text{[18]}\) Epidemiological study data have demonstrated a correlation between poor PPG control and development of cardiovascular disease,\(^\text{[19]}\) retinopathy, cognitive dysfunction, and cancer.\(^\text{[12]}\)

**Treatment Options: Rationale for Premixed Insulin**

The progressive decline in β-cell function, which occurs years before T2D is diagnosed,\(^\text{[18]}\) means that many patients will eventually require insulin,\(^\text{[1,21]}\) long considered the most effective antihyperglycemic medication available.\(^\text{[22]}\) Substantial barriers to initiating insulin include the fear of hypoglycemia and weight gain;\(^\text{[23]}\) it is therefore important to weigh glycemic benefits and hypoglycemia/weight gain risk when choosing an insulin regimen. There are three types of insulin therapy available for T2D: basal only, basal plus prandial (with premixed insulin or self-mixed basal–bolus insulin), and prandial only. While basal insulin is recommended in Europe and the USA, premixed insulin is the initial choice for 75\% of South Asian patients\(^\text{[24]}\) and the most widely prescribed treatment in Asia.\(^\text{[1]}\) The simple nature of the regimen suits its use in primary care practice and in populations with different dietary habits and cultures; these constitute key reasons for its widespread use in Asia.\(^\text{[3,25,26]}\) Premixed insulins comprise basal and prandial insulins in one injection, making them convenient to administer. Treatment can be intensified from once (od) to 3 times daily (tid) and can be used in insulin-naive patients.\(^\text{[27,28]}\)

**Literature Appraisal**

This review summarizes randomized controlled trials (RCTs) and observational studies evaluating efficacy and safety of two commonly used premixed insulin analogs for T2D: BIAsp 30 and LM 25/50. A literature search was conducted using PubMed with the search terms “efficacy and safety of BIAsp odds ratio (OR) BIAsp in type 2 diabetes” and “efficacy and safety of biphasic insulin LM OR Humalog Mix in type 2 diabetes” over the past 10-year period.\(^\text{[29]}\) The initial search returned 88 citations (BIAsp, 63; LM, 25). Articles were excluded if they evaluated only patient-reported outcomes, were post hoc analyses not relevant to the focus of this review, or they comparative studies with incretin mimetics. Cost-benefit analyses are important; however, the inclusion of these was beyond the scope of the current review. While insulin pump therapy is available in India,\(^\text{[29]}\) relevant studies are not discussed as neither BIAsp 30 nor LM 25/50 is approved for insulin pump use.

**Biphasic Insulin Aspart 30**

BIAsp 30 comprises 30% soluble rapid-acting insulin aspart (IAsp; prandial component) and 70% intermediate-acting crystallized protamine-complexed IAsp (basal component).\(^\text{[16]}\) BIAsp 50 and BIAsp 70 are available for patients who require more prandial insulin; however, these formulations are not the focus of this review. BIAsp 30 is a well-established T2D treatment, available
since 2002, which is associated with a wealth of clinical data from RCTs and observational studies of its efficacy and safety compared with other oral glucose-lowering therapies in a diverse range of patient populations.

Overview of Randomized Controlled Trials of Biphasic Insulin Aspart 30

Compared with basal and basal–bolus insulin regimens

Table 1 provides an overview of efficacy and safety data for BIAsp 30 compared with basal or basal–bolus insulin collated from 11 RCTs in patients of differing ethnicities.[31–40] Notably, there tended to be greater HbA1c reductions in studies comparing BIAsp 30 and the basal insulin glargine in insulin-naive patients.[31–34] Yang et al. reported that BIAsp 30 was noninferior to glargine in an Asian population and demonstrated significantly lower PPG levels 2 h postmeal without increased risk of hypoglycemia or weight gain.[35] Comparisons of BIAsp 30 and basal–bolus regimens meanwhile showed similar (nonsignificant treatment-group differences) HbA1c reductions.[38,39]

As might be expected, greater reductions in glucose levels were associated with an increased risk of hypoglycemia (in all but one study).[34] Where a significantly greater reduction in HbA1c was reported for BIAsp 30 than glargine, more patients experienced a hypoglycemic event (HE) (minor) or there was a greater relative risk of an event.[31–33] In terms of change in body weight, BIAsp 30 and all comparators led to an increase from baseline, with no difference between study groups.[31–40]

Compared with biphasic human insulin

In all but one study, there was no significant difference in HbA1c between BIAsp 30 and biphasic human insulin (BHI) (Table 2).[41–44] In one single-center study of obese, insulin-naive patients with T2D, a significant difference in change in HbA1c from baseline favored BIAsp 30 combined with metformin at 3 months.[45]

Significant differences favoring BIAsp 30 over BHI 30 were reported for PPG levels in the three studies evaluating this measure.[42,44,46] In terms of safety, there were generally no treatment differences for weight change or hypoglycemia (Table 2). An exception was a 24-month study, which demonstrated a significant reduction in year 2 with BIAsp 30 twice daily (bid) versus BHI 30 bid for major hypoglycemia.[44] Also in terms of safety, a Japanese study found switching from BHI 30 to BIAsp 30 was associated with improved postprandial hyperglycemia (measured by 1,5-anhydroglucitol) and decreased cardio-ankle vascular index (a reflection of arterial stiffness).[47]

Compared with oral glucose-lowering therapies

Most of the studies comparing BIAsp 30 od, bid, or tid with oral antidiabetic drugs (OADs) reported a significant HbA1c reduction favoring premixed insulin regimens [Table 3].[48–51] These studies demonstrated additional benefits for BIAsp 30 over comparator OADs in terms of PPG levels [Table 3]. One study comparing BIAsp 30 bid with glibenclamide (both plus metformin) in patients uncontrolled on prior OADs demonstrated no treatment difference in glycemic control.[52] Nevertheless, in a subgroup of patients with HbA1c ≥9% at baseline, BIAsp 30 was associated with significantly greater glycemic control than glibenclamide plus metformin (P < 0.05).

In general, few major HEs were reported for treatments; however, BIAsp treatment tended to be associated with more minor HEs.[48–51] Likewise, the effect on weight favored OADs, including glibenclamide plus metformin and metformin/pioglitazone, over BIAsp.[49,52]

Overview of Key Observational Studies of Biphasic Insulin Aspart 30

While RCTs provide the most rigorous means of determining a cause-effect relationship between treatments and outcomes,[53] observational, nonrandomized studies have an important and complementary role, allowing recruitment of larger patient cohorts in a setting more closely reflecting clinical practice. As such, they can help corroborate RCT results.

A number of such studies (i.e. IMPROVE[54] and PRESENT[55]) have examined the safety and effectiveness of BIAsp 30 across different countries and ethnicities. Collectively, these 6 months trials demonstrated improved glycemic control, as shown by reductions in HbA1c, FPG, and PPG levels from baseline, in patients initiating insulin with, or switching to, BIAsp 30.[54,55] Similar findings have been observed in the Acheive study, a prospective, multicenter, open-label, noninterventional, 24-week study of 66,726 patients from 30 countries across four continents, using insulin analogs (including BIAsp 30, insulin detemir, and IAsp).[54] Numerous country-specific findings from Acheive have shown improvements from baseline to week 24 in HbA1c, PPG, hypoglycemia, and quality of life.[57–60]

Biphasic Insulin Lispro Mix 25/50

LM 25 comprises 25% rapid-acting insulin lispro and 75% intermediate-acting insulin lispro protamine suspension. Also available is LM 50, which comprises 50% rapid-acting lispro and 50% lispro protamine suspension.[61] Numerous
**Table 1: Randomized controlled trials comparing biphasic insulin aspart 30 with (a) basal and (b) basal–bolus insulin regimens in type 2 diabetes**

### (a) basal

| Reference    | Study design                                | Patients                                                                 | HbA1c | PPG | Hypoglycemia | Mean body weight change |
|--------------|---------------------------------------------|--------------------------------------------------------------------------|-------|-----|--------------|------------------------|
| Raskin et al.[31] | 28-week, OL, MC, R; BIAsp 30 bid (n=117) versus glargine od (n=116) | Insulin-naive, uncontrolled on OADs (n=233) | Significantly greater reduction with BIAsp 30 versus glargine (~2.79 vs. −2.36, P<0.01) | 66% versus 40% achieved HbA1c target <7% (P<0.001) | Sum of three prandial PG increments: 97.4 versus 129.6 mg/dL (P<0.05) | Minor: 43% versus 15% (P<0.05) | Major: 1 episode (glargine) | Increased in both groups: 5.4 kg versus 3.5 kg (P<0.01) |
| Kann et al.[32] | 26-week, M, O-L, R; BIAsp 30 bid + metformin (n=128) versus glargine od + glimepiride (n=127) | Insulin-naive (n=258) | Significantly greater reduction with BIAsp 30 versus glargine (between treatment difference −0.5%; P=0.0002) |  | Mean prandial PG increment: 1.4 mmol/L versus 2.2 mmol/L (P=0.0002) | Minor: 20% versus 9% (P<0.05) | Major: 1 episode in each group | 0.7 kg versus 1.5 kg (P<0.0001 vs. baseline for comparator only) |
| Strojek et al.[33] | 26-week, M, O-L, R, P-G; BIAsp 30 od (n=239) versus glargine od (n=241) both combined with metformin + glimepiride | Insulin-naive (n=480) | Significantly greater reduction with BIAsp 30 versus glargine (between-treatment difference −0.2%; P=0.029) | Greater between-treatment difference in Asian versus Caucasian population (P=0.016) | Lower PG levels postdinner (treatment difference: −0.52 mmol/L; P=0.04) and at bedtime: −0.78 mmol/L (P<0.01) | RR of any HE: 6.5 ep/year versus 4.8 ep/year (1.4; P=0.034) | No difference between treatments in Asian sub-population | No difference between treatments (data not reported) |
| Kalra et al.[34] | 26-week, M, O-L, R, P-G; BIAsp 30 od (n=76) versus glargine od (n=79) both combined with metformin + glimepiride | Asian, insulin-naive (n=155) | | | PG at bedtime was lower with BIAsp 30 (P=0.0078) | Minor: 39.5% versus 30.4% (P=NS) | Major: 1.3% versus 2.5% (P=NS) | Increased in both groups: 0.80 kg versus 1.16 kg (P=NS) |
| Yang et al.[35] | 24-week, M, R, O-L, P-G; BIAsp 30 od (n=261) versus glargine od (n=260) both combined with metformin + glimepiride | Chinese and Japanese insulin-naive (n=521) | Noninferiority demonstrated with BIAsp 30 versus glargine (between-treatment difference −1.28 mmol/mol) | | Lower PG levels postdinner: 1.51 mmol/L treatment difference (P<0.001) | All HEs: 59.4% versus 56.9% (P=NS) | Between-treatment difference (−0.12 kg; P=NS) | |
| Holman et al.[36] | 3-year, O-L, R, M; BIAsp 30 bid (n=235), prandial IAsp tid (n=239), basal IDet od or bid (n=234) | Uncontrolled on OADs (n=708) | No significant difference between treatments (−1.3 vs. −1.4 [IAsp] and −1.2 [IDet]; P=NS) | 49.4% versus 67.4% (P<0.001) and 63.2% (P<0.02), respectively, achieved HbA1c target ≤7% | No significant difference between groups: 49.4% (BIAsp) versus 51.0% (IAsp) and 44.0% (IDet) | No significant difference between treatments (data not reported) | Increased in all groups: 5.7 kg versus 6.4 kg [IAsp] and 3.6 kg [IDet]; P=0.005 vs. BIAsp |
| Ligthelm et al.[37] | 24-week, O-L, P-G, R; BIAsp 30 bid + metformin versus glargine od + metformin and secretagogs | Uncontrolled on basal insulin + OADs (n=137) | No significant difference between treatments: −1.3% versus −1.2% (difference of −0.06%; P=NS) | Glucose increment averaged over 3 meals was lower with BIAsp 30 (treatment difference: −17.8 mg/dL; P=0.001) | Minor: 6.4 events/patient/year versus 3.4 events/patient/year (P<0.05) | Increased in both groups: 3.1 kg versus 1.4 kg (P=0.0004) | |
| Ligthelm et al.[38] | 16-week, OL, MC, R; BIAsp 30 tid (n=196) vs basal-bolus IAsp + NPH qid (n=198) | Uncontrolled on od or bid insulin (n=394) | Non-inferiority demonstrated with BIAsp vs comparator: Mean HbA1c at week 16: 7.81 versus 7.86% (P=NS) | No significant difference in prandial PG increment profiles | No significant difference in HES: Major: 3.1% versus 1.0% (P=NS) | ~2 kg increase in both treatment groups | |
| Hirao et al.[39] | 6-month, M, O-L, R; BIAsp 30 bid (n=80) versus IAsp tid/NPH (multiple injections) (n=80) | Japanese, insulin-naive (n=160) | No significant difference between treatments: reduction of −2.5% in both treatment groups (P=NS) | No data reported | No major HES reported | Increase in BMI: 1.47 kg/m² versus 0.69 kg/m² (P<0.05) | |

Contd...
reports from RCTs and observational studies, albeit fewer than recovered for BIAsp, demonstrate the efficacy and safety of LM 25 and LM 50 in T2D in Eastern and Western patient populations.\[62-71\] The following provides a brief review of findings for insulin-treated and insulin-naive patients.

**OVERVIEW OF RANDOMIZED CONTROLLED TRIALS OF LISPRO MIX 25/50**

Compared with basal and basal–bolus insulin regimens

Table 4 outlines key results of studies of LM 25 and LM 50 compared with basal or basal–bolus insulin regimens in patients uncontrolled on prior therapy with/without insulin. In studies comparing LM 25 or LM 50 with glargine, greater HbA1c reductions were reported, and PPG control was significantly improved with premixed insulin.\[62,64,66,69\] In the 24-week initiation phase of the Durability of Basal versus LM 75/25 Insulin Efficacy (DURABLE) study comparing LM 25 bid with glargine od, each in addition to OADs, LM 25 significantly decreased HbA1c and was associated with lower PPG levels after morning and evening meals.\[66\] However, the incidence of hypoglycemia was significantly greater with LM 25, as was weight gain. In the maintenance phase of DURABLE, patients reaching target HbA1c ≤7.0% at the end of the 24-week initiation phase were monitored for up to an additional 24 months.\[68\] This long-term follow-up showed a significantly greater proportion of patients treated with LM rather than insulin glargine maintained HbA1c goals and maintained goals for significantly longer. Furthermore, at study end, there was no difference between treatments regarding hypoglycemia and weight gain. In a recent post hoc analysis of DURABLE that examined the impact of race/ethnicity on the efficacy and safety of insulin regimens, significant differences were observed in the degree of reduction in HbA1c (smaller) and the proportion of patients reaching glycemic targets of <7% (fewer) in Asian compared with Caucasian patients.\[71\] Moreover, weight gain and rate of hypoglycemia were lower in Asian patients irrespective of treatment. These results demonstrate that racial/ethnic differences in outcomes are important considerations when designing insulin-based treatment plans.

Of three studies comparing LM 25 or LM 50 with glargine plus lispro, two showed no significant differences in HbA1c levels,\[67,70\] and one showed significantly better reduction with the basal–bolus regimen over LM 50 tid.\[63\]

Compared with biphasic human insulin or oral glucose-lowering therapies

The literature search failed to retrieve any relevant publications assessing LM 25/LM 50 with BHI or with OADs.

**OVERVIEW OF KEY OBSERVATIONAL STUDIES OF LISPRO MIX 25/50**

As the literature search did not retrieve any observational studies evaluating LM 25, LM 50 is the focus of this section.

The effect of LM 50 tid versus lispro tid plus sulfonylureas (SUs) was evaluated over 24 weeks in an observational, interventional trial of 31 Japanese patients with T2D poorly controlled with submaximal SU doses.\[73\] While there was a significant improvement in HbA1c from baseline to week 24 in both treatment groups (P < 0.00001), a similar proportion of patients achieved target HbA1c <7.0% (LM 50, 67%; prandial–bolus, 69%). Significantly fewer minor HEs occurred with LM 50 versus lispro (0.60 vs. 4.48 episodes/person/year; P = 0.03); however, weight gain significantly increased from baseline with the premixed treatment (P < 0.05) but remained unchanged in the comparator group.
**Table 2: Randomized controlled trials comparing biphasic insulin aspart 30 and biphasic human insulin 30 in type 2 diabetes**

| Reference | Study design | Patients | HbA1c | PPG | Hypoglycemia | Mean body weight change |
|-----------|--------------|----------|-------|-----|--------------|------------------------|
| Velojic-Golubovic et al.\(^{[41]}\) | 3-month, S-C; BIAsp 30 bid \((n=20)\) versus BHI 30 bid \((n=30)\), each + metformin | Insulin-naive, obese \((n=50)\) | Significant difference between BIAsp 30 versus BHI 30: decrease from baseline -2.50% versus -1.18% (treatment difference 1.33%; \(P<0.05\)) 65% versus 30% metformin <7% target \((P<0.05)\) | Decreased by 6.38 mmol/L versus 4.34 mmol/L \((P<0.05)\) | Total: 6 episodes (1 major versus 14 episodes (4 major); \(P=NS\)) | 0.3 kg versus 1.2 kg \((P\ value\ not\ reported)\) |
| Boehm et al.\(^{[41]}\) | 24-month (initial 3 months + 21-month extension), MC, R, C; BIAsp 30 bid \((n=58)\) versus BHI 30 bid \((n=67)\) | \(n=190\) \((n=125\ entered\ extension)\) | No significant difference between BIAsp 30 and BHI 30 at 24 months (BIAsp-BHI: 0.03%; \(P=NS\)) | Not reported | Major HEs Year 1: 5% versus 8% \((P=NS)\) Year 2: 0% versus 10% \((P=0.04)\) | 0.05 kg versus 2.00 kg \((P=NS)\) |
| Abrahamian et al.\(^{[41]}\) | 24-week, M, O-L, R, P-G; BIAsp 30 tid \((n=89)\) versus BHI 30 bid \((n=88)\) | \(n=177\) | No significant difference between BIAsp 30 versus BHI: Decreased from 9.8% at baseline to 7.6% versus 7.7% after 24 weeks \((P=NS)\) | Postlunch: 156 mg/dL versus 176 mg/dL \((P=0.0289)\); postdinner: 154 mg/dL versus 182 mg/dL \((P=0.0022)\) | Minor: 130 episodes versus 185 episodes \((P\ value\ not\ reported)\) Major: 2 episodes versus 0 episodes | Not reported |
| McNally et al.\(^{[41]}\) | M, R, D-B, 2-period \((2\times16\ weeks)\), crossover; BIAsp 30 bid \((n=80)\) versus BHI 30 bid \((n=80)\) | Pretreated with insulin \((n=160)\) | No significant difference between treatment arms: Decreased from 7.46% to 7.28% versus 7.22% (treatment difference 0.06%; \(P=NS)\) | Not reported | Minor: 90% versus 84% Major: 2 episodes versus 7 episodes \((P\ value\ reported)\) | Not reported |
| Temizel et al.\(^{[41]}\) | 1-year, retrospective; BIAsp 30 bid \((or\ biphasic\ insulin lison) \((n=71)\) versus BHI 30 bid \((n=69)\) | \(n=140\) | No significant difference between premixed insulin and BHI 30 | Not reported | Mild: 0.72 events/person/month versus 0.65 events/person/month \((P=NS)\); Severe: 0.06 events/person/month versus 0.04 events/person/month \((P=NS)\) | Increased in both groups: 2.08 kg versus 2.29 kg \((P=NS)\) |
| Schmoelzer et al.\(^{[41]}\) | S-C, OL, R; crossover; BIAsp 30 od versus BHI 30 od | \(n=12\ already\ receiving\ premixed\ insulin\) | Not reported | Maximum increase of PPG reduced \((5.27\ mmol/L\ vs. 7.10\ mmol/L; \(P=0.007)\) | Not reported | Not reported |

**COMPARATIVE STUDIES OF BIPHASIC INSULIN ASPART 30 AND LISPRO MIX 25/50**

Despite the breadth of data available for premixed insulin regimens, there are very few data comparing BIAsp 30 with LM 25 or LM 50. Indeed, in the last 15 years (search criteria extended for these data), just three studies have been published comparing these therapies.\(^{[73-75]}\)

In an open-label, randomized, single-dose, three-way crossover trial, 61 insulin-treated patients received BIAsp 30, BHI 30 or LM 25 immediately before a test meal.\(^{[73]}\) PPG control assessed by serum glucose excursions 0–5 h postmeal was significantly improved with BIAsp 30 versus BHI 30 and LM 25, with PPG levels 17% lower compared with BHI 30 (16.6 vs. 20.1 mmol/L; \(P < 0.001\)) and 10% lower compared with LM 25 (16.6 vs. 18.9 mmol/L; \(P < 0.05\)). A total of 53 HEs were reported, most of which were mild. By contrast, a 12-week, open-label, two-period, crossover study in 137 patients who had previously received insulin demonstrated no significant difference between BIAsp 30 bid and LM 25 bid in glycemic control, with treatments providing comparable reductions in HbA1c at week 12.\(^{[74]}\) There were also no significant treatment differences for hypoglycemia (BIAsp 30, 0.69 episodes/month; LM 25, 0.62 episodes/month; \(P = NS)\).
The third study was not a direct comparison of efficacy between BIAsp 30 and LM 25 or LM 50, but a comparison of LM 50 tid compared with progressive titration of LM 25 or BIAsp 30 bid, administered together with metformin.[38] This 16-week, randomized, parallel-group study of 302 patients failing to achieve glycemic control with BIAsp 30 or LM 25 bid demonstrated no significant treatment difference in mean change from baseline in HbA1c (−1.0% with LM 50 tid, −0.82% with BIAsp 30/LM 25 bid; P = NS). While no statistically significant difference was observed between treatments for hypoglycemia, the tid group was associated with greater weight gain than the bid group (1.3 vs. 0.4 kg, respectively; P = 0.0009).

There are too few studies to form any conclusions regarding the comparative efficacy and safety of BIAsp 30 and LM 25/LM 50. Whether additional, comparative, studies are required is questionable given that a systematic review of three head-to-head trials of premixed insulin analogs revealed no differences in FPG, PPG, or HbA1c reduction between BIAsp 30, LM 25, and LM 50.[74]

**DISCUSSION**

This review provides an overview of RCTs and observational studies comparing the efficacy and safety of BIAsp 30 and LM 25/LM 50 with other insulin therapies and OADs in patients with T2D. Although BIAsp 50 and BIAsp 70 are available for patients who require more prandial/bolus insulin, BIAsp 30 is the focus of this review given the experience accumulated over the years of use with this formulation. Overall, premixed insulin analogs were

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**Table 3: Randomized controlled trials comparing biphasic insulin aspart 30 and oral glucose-lowering therapies in type 2 diabetes**

| Reference | Study design | Patients | HbA1c | PPG | Hypoglycemia | Mean body weight change |
|-----------|--------------|----------|-------|-----|--------------|------------------------|
| Raz et al.[49] | 18-week, MC, O-L, P-G; BIAsp 30 bid + PIO (n=93) versus GLIB + PIO (n=93) and BIAsp 30 bid (n=97) | Uncontrolled on SU (GLIB) (n=283) | Uncontrolled on SU (GLIB) (n=283) | Significant difference between BIAsp 30 + PIO versus GLIB + PIO (−0.64%; P=0.005) and between BIAsp 30 + PIO versus BIAsp 30 (−0.60%; P=0.008) | Postbreakfast, postlunch, and postdinner lower with BIAsp 30 + PIO versus GLIB + PIO (P<0.05); postdinner versus BIAsp 30 (P<0.05) | No major HEs: 15% (BIAsp 30 + PIO) versus 3% (GLIB + PIO) and 12% (BIAsp 30); no P values reported | Not reported |
| Bebakar et al.[50] | 26-week, MC, O-L, R; BIAsp 30 (od with up titration to bid) + OAD (n=128) versus OAD mono (n=63) | Insulin-naive (n=191) | Insulin-naive (n=200) | Significant greater reduction with BIAsp 30 od versus OAD mono and with BIAsp 30 od versus OAD mono: (BIAsp 30 od −1.24% and BIAsp 30 bid −1.34% vs. OAD mono −0.67%; P<0.01) | Greater reductions at Week 13 with BIAsp 30 od after morning and evening meals (P<0.05) | 54% versus 30% (P<0.005) - all classified as minor except one major HE in each group | Increase with BIAsp 30 od and bid versus decrease with OAD (0.96 kg and 1.53 kg vs. −0.18 kg; P<0.005) |
| Raskin et al.[51] | 34-week, MC, O-L, P-G; BIAsp 30 bid + metformin/PIO (n=102) versus metformin/PIO (n=98) | Insulin-naive (n=200) | Insulin-naive (n=200) | Significantly greater reduction with BIAsp 30 versus OADs (change from baseline −1.5% vs. −0.2%; P<0.001) | HbA1c ≥6.5%: 59% versus 12% (P<0.001); <7.0%: 76 versus 24% (P<0.001) | Reduced with BIAsp 30 at all-time points (P<0.05 vs. metformin/PIO) | Greater increase with BIAsp 30 (4.6 kg vs. 0.8 kg; P<0.001) |
| Ushakova et al.[52] | 16-week, MC, O-L, P-G; BIAsp 30 tid (n=104), BIAsp 30 bid + metformin (n=100) versus OADs (n=104) | Insulin-naive, uncontrolled on OADs (n=308) | Insulin-naive, uncontrolled on OADs (n=308) | Significantly greater reduction with BIAsp 30 and BIAsp 30 + metformin versus OADs (−2.9% and −3.0%, respectively, vs. −2.1%; both P<0.001) | Improved with BIAsp 30 and BIAsp 30 + metformin (−6.32 and −6.44 mmol/L vs. −3.59 mmol/L; both P<0.001) | No major HEs: Minor: 4 and 9 episodes (BIAsp 30 + metformin) versus 1 episode | Increased with BIAsp 30 and BIAsp 30 + metformin (1.71 kg and 1.50 kg versus −0.75 kg) |
| Kvapil et al.[53] | 16-week, MC, OL, R, P-G; BIAsp 30 bid + metformin (n=108) versus GLIB + metformin (n=114) and BIAsp 30 bid (n=107) | Uncontrolled on metformin (n=341) | Uncontrolled on metformin (n=341) | No significant difference between BIAsp 30 versus GLIB + metformin (0.20%; P=NS) | No significant difference between groups, except postlunch (−0.74 mmol/L with GLIB + metformin vs. BIAsp 30; P>0.05) | No major HEs: Minor HEs: 23 episodes (BIAsp 30 + metformin) versus 28 (GLIB + metformin) and 20 episodes (BIAsp 30); P=NS | Weight increased in all groups; greater with BIAsp 30 versus GLIB + metformin (P<0.001) |

*Total population results included only; If HbA1c >8.5% or fasting plasma glucose >7 mmol/L at week 14. BIAsp: Biphasic insulin aspart, bid: Twice daily, GLIB: Glibenclamide, HE: Hypoglycemic episode, od: Once daily, OL: Open-label, MC: Multicenter, P-G: Parallel-group, PIO: Pioglitazone, PPG: Postprandial glucose, R: Randomized, SU: Sulfonylurea, T2D: Type 2 diabetes, tid: Three times daily, HbA1c: Glycated hemoglobin, OAD: Oral antidiabetic drug, NS: Not significant.
**Table 4: Randomized controlled trials comparing lispro mix 25/lispro mix 50 with (a) basal and (b) basal–bolus insulin regimens in Type 2 diabetes**

(a) basal

| Reference            | Study design                        | Patients | HbA1c | PPG          | Hypoglycemia | Mean body weight change |
|----------------------|-------------------------------------|----------|-------|--------------|--------------|-------------------------|
| Malone et al.[62]    | MC, R, prospective, O-L, crossover (2x 16-week); LM 25 bid (n=52) versus glargine od (n=53), both with metformin | Insulin-naive (n=105) | Significantly greater decrease with LM 25 versus glargine (−1.3% vs. −0.9%; P=0.003) ≤7% target HbA1c: 42% versus 18%; P<0.001 | Similar postlunch but lower postbreakfast (156.4 mg/dL vs. 171.1 mg/dL; P=0.012) and dinner (164.8 mg/dL vs. 193.8 mg/dL; P<0.001) | Low in both groups, but higher with LM 25 (0.68 episodes/patient/30 days vs. 0.39 episodes/patient/30 days; P<0.05) | Similar gain in both groups (2.8% vs. 2.9%; P=NS) |
| Robbins et al.[69]   | 24-week, MC, R, O-L, P-G; LM 50 tid + metformin (n=157) versus glargine od + metformin (n=158) | Previously treated with OADs (n=315) | Significantly greater reduction with LM 50 versus glargine (−0.7% vs. −0.4%; P<0.001) HbA1c ≤7%: 56.3% versus 39.7% (P=0.005); ≤6.5%: 46% versus 21% (P<0.001) | Lower with LM 50 (postbreakfast: 8.7 mmol/L vs. 9.2 mmol/L; P<0.05; postlunch: 8.4 mmol/L vs. 9.8 mmol/L; P<0.001; postsupper: 8.7 mmol/L vs. 10.7 mmol/L; P<0.001) | Overall HEs: 28.8% versus 17.7% (P=0.02) | Weight gain with LM 50 (1.2 kg) versus weight loss (−0.5 kg; P<0.001) |
| Milicevic et al.[66]  | 24-week, MC, R, O-L, P-G; LM 50 (pm) (n=68) versus. Glib + NPH insulin (n=67) | Uncontrolled on OADs (n=135) | Significantly greater reduction with LM 25/LM 50 versus NPH (−1.3% vs. −0.5%; P<0.01) | Lower with LM 25/LM 50 (11.13 mmol/L vs. 14.46 mmol/L; P=0.0001) | Higher with LM 25/LM 50 (0.22 episodes/patient/30 days vs. −0.08 episodes/patient/30 days; P=0.037) | Weight gain similar for both groups (1.42 kg vs. 1.20 kg; P=NS) |
| Buse et al.[65]      | 24-week, MC, R, O-L, P-G; LM 25 bid (n=1045) versus glargine od (n=1046), both + OADs | Insulin-naive (n=2091) | Significantly greater reduction with LM 25 versus glargine (−1.8% vs. −1.7%; P=0.005) HbA1c <7%: 47.5% versus 40.3%; P<0.001 | Lower levels with LM 25 after morning (167 mg/dL vs. 172 mg/dL; P=0.05) and evening (163 mg/dL vs. 176 mg/dL; P<0.001) | Overall: 57.1% versus 51.8% (P=0.016) | Weight gain 3.6 kg versus 2.5 kg (P<0.001) |
| Sakharova et al.[68] | 6-month, S-C, O-L, crossover; LM 25 bid versus glargine od | Uncontrolled on OADs (n=16) | Significantly greater reduction with LM 25 versus glargine (−2.3% vs. −1.7%; P=0.009) | 23% lower with LM 25 (153 mg/dL vs. 199 mg/dL; P=0.001) | No major HEs; no significant difference between groups in minor HEs (3.2 vs. 0.9; P=NS) | Weight gain not significantly different between groups (2.4 kg vs. 1.7 kg; P=NS) |
| Buse et al.[65]      | ≤24-month, MC, R, O-L, P-G; LM 25 bid (n=473) versus glargine od (n=419), both + OADs | Insulin-naive (patients had completed 24-week initiation study with HbA1c ≤7%) | Significantly longer time of maintaining target HbA1c goal ≤7% longer with LM 25 versus glargine (16.8 months vs. 14.4 months; P=0.05) More LM 25 patients maintained HbA1c goal (43% vs. 35%; P=0.006) | Lower levels with LM 25 evening PPG (P<0.001) | Overall: 49.9% versus 45.3% (P=NS) | No difference during maintenance phase (1.6 kg vs. 1.8 kg; P=NS) |

(b) basal–bolus

| Reference            | Study design                        | Patients | HbA1c | PPG          | Hypoglycemia | Mean body weight change |
|----------------------|-------------------------------------|----------|-------|--------------|--------------|-------------------------|
| Bowering et al.[63]  | 48-week, MC, O-L, R; LM 25 od to tid (n=214) versus glargine-lispro (n=212) | Insulin-naive, uncontrolled on OADs (n=426) | No significant difference between LM 25 and glargine + lispro (LM 25-glargine + lispro difference: −0.4%) | No difference between groups in mean change from baseline (5.24 mmol/L vs. 4.89 mmol/L; P=NS) | No difference in overall rate/30 days (1.71 vs. 1.96) | Weight gain of 2.78 kg versus 2.92 kg (no P value reported) |
| Jain et al.[67]      | 36-week, MC, O-L, R; LM 50 od to tid (n=242) versus glargine + mealtime lispro (n=242) | Uncontrolled on OADs (n=484) | No significant difference in reduction between treatment arms (−1.76% vs. −1.93%; P=NS) | Evening PPG lower with LM 50 (167.4 mg/dL vs. 176.4 mg/dL; P=0.010) | No difference in overall incidence (74.5% vs. 74.6%; P=NS) | No difference between groups (3.09 kg vs. 3.19 kg; P=NS) |

Contd...
associated with improved glycemic control, as evidenced by reductions from baseline in both HbA1c and in PPG versus comparator regimens.\cite{31,35,37,42,45,46,48-51,62,64-66,68} As such, these data highlight the importance of targeting PPG with an appropriate regimen, and the contribution this makes to the overall achievement of glycemic control. In addition, DURABLE demonstrated long-term treatment with a premixed insulin analog provided modestly improved durability of glycemic control compared with glargine.\cite{68}

In general, however, studies found premixed insulin tended to increase minor hypoglycemia and weight gain compared with basal insulin comparators. While such effects present challenges in T2D, these issues can be managed simply by implementing less aggressive insulin titration schedules, regular meals, and dietary/exercise intervention. Regarding comparisons of the insulin analog BIAsp 30 with BHI 30, the PPG and hypoglycemia benefits observed with the premixed insulin analogs may render them the preferred treatment modality.\cite{41,42,45,46} This would be especially true in Asia where a large proportion of patients with diabetes are treated with BHI.

In addition to RCTs, large observational trials are beneficial as they investigate the effectiveness and safety of treatments in a real-life setting (i.e. day-to-day clinical practice). Recent findings from the large, observational A1chieve study are particularly noteworthy as they showed that, across four continents, patients with T2D treated with BIAsp 30 achieved improvements from baseline, not only in glycemic control, but also in quality of life.\cite{57-60} An improvement in hypoglycemia with BIAsp 30 was also reported in this and other observational trials.\cite{54,55,57-60}

The need to individualize treatment regimens is key in many diseases, including T2D, and is illustrated by the results of a post hoc analysis of DURABLE. In this analysis, significant differences were observed between race/ethnic groups in the effect of LM 25 and insulin glargine (e.g., smaller reductions in HbA1c for Asian compared with Caucasian patients).\cite{71} As highlighted in diabetes management guidelines, treatment individualization, focusing on patient preference (including ethnic and cultural needs) is crucial to treatment success.\cite{1} This is particularly relevant for patients requiring insulin, in terms of when and how to initiate and intensify therapy, and choice of regimen. Another important consideration when initiating and intensifying insulin therapy is the cost of treatment in relation to benefits of glycemic control and the risk of short- and long-term complications. There is evidence that insulin analogs can offer cost-effective treatment, having been associated with improved clinical outcomes and an increase in quality-adjusted life-years.\cite{77-80}

Together, these data indicate that premixed insulin regimens are appropriate and convenient treatments for most patients with T2D, offering flexibility in dosing schedule for people with regular eating patterns, and requiring fewer injections compared with basal–bolus regimens. These benefits render premixed insulin analogs the treatment of choice in many Asian countries, including India, where a large proportion of patients are treated in primary care practice.\cite{3}

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