

**Bon Secours Richmond  
Pharmacy & Therapeutics Committees  
Biphasic Insulin Mixes:  
Humalog® Mix 75/25, NovoLog® Mix 70/30, Novolin 70/30**

**Recommendations: MEC Approved MRMC, SMH**

- NovoLog Mix 70/30 will be used in place of Humalog Mix 75/25 and Novolin 70/30. NovoLog Mix 70/30 improves postprandial blood sugar control compared to Novolin 70/30 and control is similar to Humalog 75/25. NovoLog Mix 70/30 is on Premier contract and is less expensive than Humalog Mix 75/25.
- Humalog Mix 75/25 and NovoLog Mix 70/30 (rapid acting mixes) produce similar blood sugar control and may be therapeutically interchanged.
- Pharmacy will automatically substitute the most cost-effective, rapid-acting biphasic mix.
- This conversion is recommended during hospitalization only.

**Findings:**

- Insulin Aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and Insulin Lispro with amino acids in position 28 and 29 reversed. These changes reduce the tendency of the analogs to self-associate into dimers and hexamer, and increase the rate of absorption.
- Insulin aspart and lispro are faster acting but have a shorter duration of action when compared to regular insulin.
  - Very short acting insulin analogs (aspart and lispro) have been shown to reduce prandial glucose excursions
- Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection)  
Novolog Mix 70/30 (70% insulin aspart protamine and 30% insulin aspart injection)
- The most commonly prescribed premixed insulin worldwide is 70/30.
- Humalog Mix 75/25 and Novolog Mix 70/30 have two absorption phases, a rapid and a prolonged phase.
- No significant differences were found between Humalog Mix 75/25 and NovoLog 70/30 when comparing pharmacokinetic profiles or blood glucose profiles. They have a comparable duration of action to that of Humulin 70/30 (30% Regular Insulin and 70% NPH Insulin), but have a quicker onset of glucose lowering.
- Altering the ratio of soluble and intermediate-acting insulin in mixtures seems to produce little difference in both insulin concentration and blood glucose concentration when comparing adjacent formulations (10:90, 20:80, 30:70, 40:60, 50:50, fact acting: intermediate).
- Humalog Mix 75/25 and NovoLog Mix 70/30 should NOT be mixed with any other insulin products and are intended for subcutaneous administration only; these products should not be given intravenously.
- Humalog and NovoLog have been shown to be equipotent to regular human insulin, unit for unit.
- Humalog Mix 75/25 has been shown to be equipotent to regular human insulin on a molar basis (one unit of Humalog has the same glucose lowering effect as one unit of regular human insulin), but its effect is more rapid.
  - Humalog Mix 75/25 has a similar glucose-lowering effect as compared to Humulin 70/30 on a unit for unit basis.
- The rate of insulin absorption and onset of activity of Humalog Mix 75/25 and NovoLog 70/30 can be affected by site of injection, exercise, and other variables
- HbA1c is linearly related to plasma glucose levels measurements in type I diabetics with good correlation, Mean Plasma Glucose mg/dl =  $(35.6 * HbA1c) - 77.3$  ( $r=0.82$ ), using a 7 point glucose profile (pre and post meals and bedtime). Postprandial blood sugar contributes appreciably to the HbA1c (lunch and dinner > breakfast).
- HbA1c is a weighted average of blood glucose levels during the preceding 120 days. Glucose levels in the preceding 30 days contribute approximately 50% to the final result and glucose levels for 90-120 days earlier contribute only 10%.
- There are insufficient data to determine accurately the relative contribution of the FPG and PPG to HbA1c. It appears that FPG is somewhat better than PPG in predicting HbA1c especially in type 2 diabetes.
- In nondiabetic individual, plasma glucose concentration peak about 60 minutes after the start of a meal, rarely exceed 140 mg/dl, and return to preprandial levels within 2-3 hours. Absorption of ingested carbohydrate continues for at least 5-6 hours after a meal.
- Blood glucose conversion: 18 mmol/l of 1 mg/dl

	<b>NovoLog Mix 70/30 (Aspart)</b>	<b>Humalog Mix 75/25 (Lispo)</b>
<b>Onset</b>	0.5 hrs	0.25 hrs
<b>Peak</b>	2.4 ± 0.8 hrs	2.6 ± 2.4 hrs
<b>Duration</b>	4-6 hrs	4-6 hrs
<b>% of total activity occurring in first 4 hours</b>	45% ± 22%	35% ± 18%
<b>Pregnancy Category</b>	C*	B**
<b>Administration</b>	Immediately or within 10-15 minutes before a meal	10-15 minutes before or immediately after meals
<b>Components</b>	70% insulin aspart protamine and 30% insulin aspart	75% insulin lispo protamine & 25% insulin lispro
<b>Amino Acid Sequence</b>	Amino acid proline by aspartic acid in position B28	Amino acids in position 28 and 29 reversed
<b>Mixing With Other Insulins</b>	No	No
<b>Route of Administration</b>	SC	SC

Inactive ingredients are similar except mannitol in NovoLog and glycerin in Humalog.

\* NovoLog in rats and rabbits, 32 and 3 times the human dose.

\*\*Humalog in rats and rabbits, 4 and 0.3 times the human dose.

Table 1: Glycemic Parameters at the End of Treatment [Mean (SD)]

	NovoLog Mix 70/30	Novolin 70/30
Type 1, N=92		
Fasting Blood Glucose (mg/dL)	173 (62.3)	141 (58.7)
1.5 Hour Post Breakfast	185 (80.1)	198 (80.1)
1.5 Hour Post Dinner	158 (76.5)	169 (65.9)
HbA1c (%)	8.4 (1.1)	8.3 (1.0)
Type 2, N=169		
Fasting Blood Glucose (mg/dL)	151 (39.2)	151 (67.6)
1.5 Hour Post Breakfast	180 (64.1)	198 (80.1)
1.5 Hour Post Dinner	166 (49.8)	189 (49.8)
HbA1c (%)	7.9 (1.0)	8.1 (1.1)

Three-month, open-label trial, BID injections

	<i>Cost per vial</i>	<b>RCH</b>		<b>MRMC</b>		<b>SMH</b>		<b>SAH</b>		<b>TOTAL</b>	
		<i>Units</i>	<i>Cost</i>	<i>Units</i>	<i>Cost</i>	<i>Units</i>	<i>Cost</i>	<i>Units</i>	<i>Cost</i>	<i>Units</i>	<i>Cost</i>
<b>Humalog 75/25</b> 830414	\$54.85	16	\$877.60	111	\$6,088.35	88	\$4,826.80	1	\$54.85	216	\$11,847.60
<b>NovoLog 70/30</b> 707327	\$33.71	3	\$101.13	13	\$438.23	10	\$337.10	4	\$134.84	30	\$1,011.30
<b>Novolin 70/30</b> 51284	\$10.63	30	\$318.90	236	\$2,508.68	112	\$1,190.56	25	\$265.75	403	\$4,283.89
Potential Cost Saving per Year by converting Humalog to Novolog										\$5,200.44	
Cost to Convert All to Novolog										\$4,735.00	

# A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes.

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**OBJECTIVE:** To study the pharmacokinetic and pharmacodynamic profiles of insulin aspart and insulin lispro in type 1 diabetic patients in a direct comparison and to investigate whether the administration of one analog results in favorable effects on prandial blood glucose control.

**RESEARCH DESIGN AND METHODS:** A total of 24 type 1 diabetic patients (age 36 +/- 8 years, 16 men and 8 women, BMI 24.3 +/- 2.6 kg/m<sup>2</sup>), diabetes duration 17 +/- 11 years, HbA(1c) 7.9 +/- 0.8%) on intensified insulin therapy were recruited into a single-center, randomized, double-blind, two-period, cross-over, glucose clamp trial. The subjects were given an individual need-derived dose of prandial insulin lispro or aspart immediately before a standard mixed meal on two different occasions separated by 4-14 days. Experiments were only performed if plasma glucose values remained stable between 5.6 and 7.8 mmol/L (101 and 140 mg/dL) during the 60-minute period before test meal. Blood samples were drawn at 15-minute intervals, from -45 minutes to time of insulin injection (0 minutes), every 10 minutes until 120 minutes, and thereafter every 20 minutes until the end of the experiment.

**RESULTS:** With respect to blood glucose excursions from time 0 to 6 hours (Exc(glu(0-6 h))) and from time 0 to 4 hours (Exc(glu(0-4 h))), the pharmacodynamic effect of insulin aspart and insulin lispro can be declared equivalent (Figure 1). This was supported by comparison with maximum postprandial blood glucose excursions (C(max(glu))) (estimated ratio aspart/lispro ANOVA [90% CI]: 0.95 [0.80-1.13], 0.97 [0.82-1.17], and 1.01 [0.95-1.07] for Exc(glu(0-6 h)), Exc(glu(0-4 h)), and C(max(glu)), respectively). For pharmacokinetic end points (maximum postprandial insulin excursions and area under the curve for insulin from time 0 to 6 h and from time 0 to 4 h), equivalence was indicated. No difference concerning absorption or elimination for time to maximal insulin concentration, time to half-maximum insulin concentration, and time to decrease to 50% of maximum insulin concentration was observed.

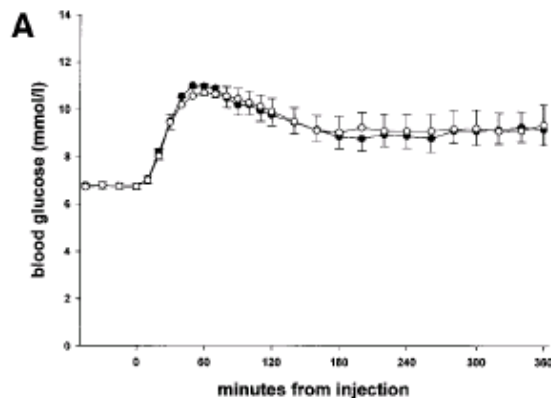


Figure 1: Blood glucose concentrations in 24 patients with type 1 diabetes after injection of insulin aspart (●) and insulin lispro (○) immediately before a standardized meal (time 0). The concentrations are expressed as means ±SE.

**Table 1—Blood glucose excursions from 0 to 6 h after a standard meal**

Exc <sub>glu(0-6 h)</sub> (mmol · l <sup>-1</sup> · min)	Aspart	Lispro
N	24	24
Arithmetic mean	1,093.1	1,221.7
SE	104.5	143.9
Geometric mean	6.9	6.9
Coefficient of variation (%)	46.8	57.7
Minimum to maximum	405.0–2,233.3	412.3–2,486.4

**Table 2—Pharmacokinetics based on 6-h serum insulin profiles**

	Aspart	Lispro	ANOVA (ratio [90% CI])
C <sub>max</sub> (pmol/l)	271.4 ± 29.3	257.6 ± 20.5	1.01 [0.95–1.11]
AUC <sub>(0-4 h)</sub> (pmol · l <sup>-1</sup> · min)	23,653.6 ± 2269.9	23,411.1 ± 1896.8	0.99 [0.90–1.08]
AUC <sub>(0-6 h)</sub> (pmol · l <sup>-1</sup> · min)	24,074.3 ± 2321.8	24,537.2 ± 2119.3	0.97 [0.88–1.06]
AUC <sub>(4-6 h)</sub> (pmol · l <sup>-1</sup> · min)	420.7 ± 113.4	1,126 ± 385.2	0.62 [0.30–1.27]

Data are means ± SE.

**CONCLUSIONS:** The data presented indicates identical pharmacodynamic and pharmacokinetic properties; therefore, no clinical difference can be expected when comparing these two analogs. This also suggest that in type 1 diabetic patients, both insulin lispro and insulin aspart are equally effective for control of postprandial blood glucose excursions.

# Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects.

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**OBJECTIVE:** To compare blood insulin levels and actions on glucose and fat metabolism in patients with type 1 diabetes after subcutaneous injection of the rapid-acting insulin analogs aspart and lispro.

**RESEARCH DESIGN AND METHODS:** Seven C-peptide-negative patients with type 1 diabetes with no diabetic complications (two men and five women) were studied at the General Clinical Research Center at Temple University Hospital two times, 1 month apart. Their plasma glucose was normalized overnight by intravenous infusion of insulin. The next morning, they received subcutaneous injections of either aspart or lispro at a dose equal to one-half of their normal daytime insulin dose ( $9.4 \pm 1.9$  U) in random order. For the next 4-5 h, their plasma glucose was clamped at approximately 5.5 mmol/l (100 mg/dL) with a variable infusion of 20% glucose. The study was terminated after 8 h. Blood samples were collected at 30 to 60-minute intervals (-120, -30, 0, 30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes).

**RESULTS:** Both insulin analogs produced similar serum insulin levels (250-300 pmol/l) at approximately 30 minutes and disappeared from serum after approximately 4 hours. Insulin aspart and lispro had similar effects on glucose and fat metabolism. Effects on carbohydrate metabolism (glucose uptake, glucose oxidation, and endogenous glucose production) peaked after approximately 2-3 hours and disappeared after approximately 5-6 hours.

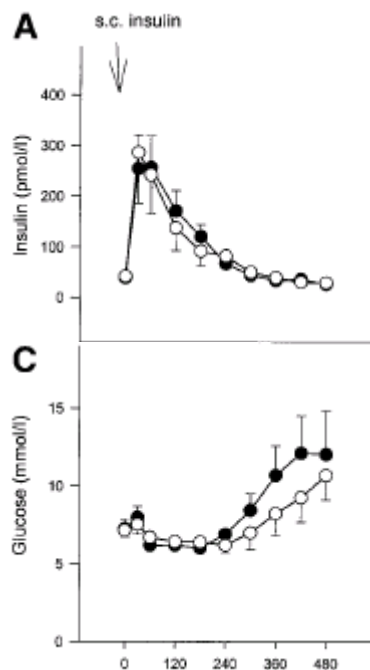


Figure 1: (A) Serum insulin levels before and after subcutaneous injection (at 0 minutes) of insulin aspart (●) or insulin lispro (○) in seven patients with type 1 diabetes. (C) Plasma glucose concentrations before and after subcutaneous injection of insulin aspart or insulin lispro in the same seven patients.

**CONCLUSIONS:** We conclude that both insulin aspart and lispro are indistinguishable from each other with respect to blood levels and that they are equally effective in correcting abnormalities in carbohydrate and fat metabolism in patients with type 1 diabetes. Both insulins produced virtually superimposable insulin concentration curves, thus supporting the notion that the bioactivity profiles of the two are interchangeable.

# Improved postprandial glycaemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes.

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**OBJECTIVE:** To compare the postprandial serum glucose control of biphasic insulin aspart 30 (BIAsp 30: 30% aspart, 70% protamine aspart) with that of biphasic insulin lispro 25 (Mix25: 25% lispro, 75% protamine lispro) and biphasic human insulin 30 (BHI 30: 30% regular insulin, 70% NPH insulin) in insulin-treated subjects with type 2 diabetes.

**RESEARCH DESIGN AND METHODS:** Open-labeled, randomized, single-dose, three-way crossover trial of 61 insulin-treated subjects with type 2 diabetes who had no significant late diabetic complications (BMI < 32 kg/m<sup>2</sup>, HbA1c < 10%, ≥ 18 years old). A single subcutaneous injection (0.4 units/kg body weight) of one of the three biphasic insulin preparations was administered in the abdomen before eating a standard breakfast on each study day. BIAsp 30 and Mix25 were injected immediately before the test meal, and BHI 30 fifteen minutes before. Fifty-five subjects completed the trial, with 45 included in the PP analysis population. The primary target of analysis was serum glucose excursion 0-5 h after a meal. Serum glucose concentration profiles were collected in 15-minute intervals from 30 minutes before the meal to 3 hours after the meal and at 30-minute intervals for the last 2 hours of the 5-hour sampling period.

**RESULTS:** The postprandial glycaemic control with BIAsp 30, as assessed by the 5-h postmeal serum glucose excursion, was superior to that with both BHI 30 and Mix25 (298.8 ± 81 vs. 361.8 ± 88.2 and 340.2 ± 109.8 mg/dL per hour, respectively; P < 0.001 and P < 0.05)(Figure 1). Compared with Mix25, there was a shorter time to C<sub>max(SG)</sub> (-11 min; P < 0.05) after treatment with BIAsp 30, however, no difference in C<sub>max(SG)</sub> between the two.

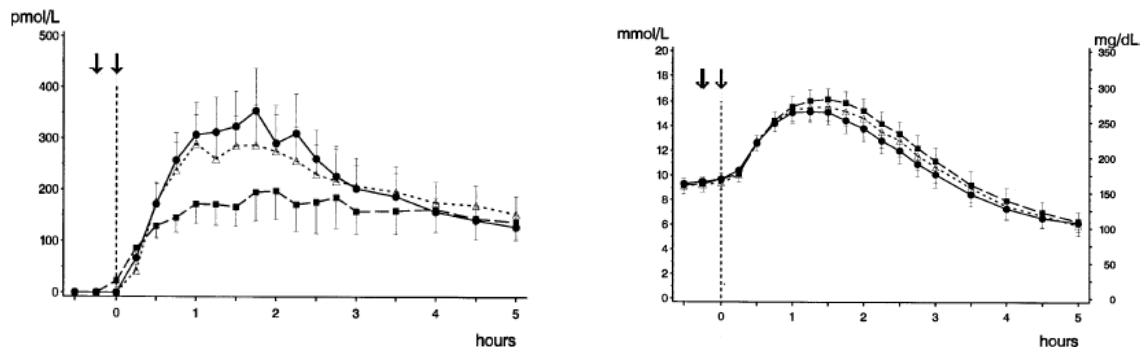


Figure 1: Mean postprandial serum insulin (left) and glucose (right) profiles for subjects with type 2 diabetes after injection of BIAsp 30 (●) and Mix25 (Δ) immediately before test meal and BHI 30 (■) 15 minutes before test meal. Arrows indicate the injection times; vertical dotted line marks the time of meal ingestion. Error bars represent 2x standard error of the mean.

**CONCLUSIONS:** The results of this trial show that postprandial glucose concentrations in individuals with type 2 diabetes can be more effectively controlled with BIAsp 30 than with either BHI 30 or Mix25. No significant difference in maximum serum insulin concentrations could be demonstrated between BIAsp 30 and Mix25, despite a tendency for higher serum insulin concentrations with BIAsp 30 from 1 to 2.5 hours. This trial only shows results after a single meal and limited data is available to establish the long-term benefits of twice-daily treatment with biphasic insulin analogs. Study supported by Novo Nordisk

**Table 1**—Results and ANOVA comparisons of BIAsp 30 (injected at mealtime) with Mix25 (injected at mealtime) and BHI 30 (injected 15 min before mealtime)

Glucose end point	Means $\pm$ SD	Ratio* between treatments (95% CI)	
		BIAsp 30 / BHI 30	BIAsp 30 / Mix25
<i>Pharmacodynamic end points:</i>			
<i>Glucose excursion</i>			
EXC <sub>0-5 (SG)</sub> (mmol/l $\times$ h)			
BHI 30	20.1 $\pm$ 4.9	0.83 (0.77; 0.90)†	
BIAsp 30	16.6 $\pm$ 4.4		0.90 (0.83; 0.98)‡
Mix25	18.9 $\pm$ 6.1		
EXC <sub>0-2 (SG)</sub> (mmol/l $\times$ h)			
BHI 30	9.4 $\pm$ 2.7	0.81 (0.71; 0.93)§	
BIAsp 30	7.7 $\pm$ 2.7		0.97 (0.85; 1.11)
Mix25	8.5 $\pm$ 3.3		
EXC <sub>2-5 (SG)</sub> (mmol/l $\times$ h)			
BHI 30	10.1 $\pm$ 3.2	0.82 (0.72; 0.94)§	
BIAsp 30	8.3 $\pm$ 2.6		0.88 (0.77; 1.00)‡
Mix25	9.7 $\pm$ 3.8		
C <sub>max (SG)</sub> (mmol/l)			
BHI 30	16.7 $\pm$ 2.6	0.95 (0.91; 1.00)‡	
BIAsp 30	15.9 $\pm$ 2.7		0.99 (0.94; 1.04)
Mix25	16.4 $\pm$ 3.2		
t <sub>max (SG)</sub> (min)			
BHI 30	88.0 $\pm$ 26.4	-13.2 (-22.2; -4.1)§	
BIAsp 30	75.1 $\pm$ 22.2		-11.3 (-20.5; -2.11)‡
Mix25	86.5 $\pm$ 26.9		
<i>Pharmacokinetic end points:</i>			
<i>Insulin</i>			
AUC <sub>0-5h (ins)</sub> (pmol/l $\times$ h)			
BHI 30	741 $\pm$ 426	1.72 (1.40; 2.10)†	
BIAsp 30	1,079 $\pm$ 535		1.07 (0.90; 1.28)
Mix25	1,031 $\pm$ 621		
C <sub>max (ins)</sub> (pmol/l)			
BHI 30	237 $\pm$ 156	2.01 (1.64; 2.46)†	
BIAsp 30	415 $\pm$ 244		1.12 (0.95; 1.34)
Mix25	360 $\pm$ 211		
t <sub>max (ins)</sub> (min)			
BHI 30	169 $\pm$ 71	-55.3 (-85.0; -25.5)†	
BIAsp 30	115 $\pm$ 59		15.15 (-11.4; 41.7)
Mix25	100 $\pm$ 41		

PK and PD parameter data are means  $\pm$  SD. The ratios and differences (with 95% CIs) refer to ANOVA analyses comparing BIAsp 30 with Mix25 and BHI 30 treatments in the PP population. \*Ratios except for t<sub>max</sub> are difference in minutes; †P < 0.001; ‡P < 0.05; §P < 0.01; ||data obtained from t = -15 to t = 285.

# Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial.

Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE.

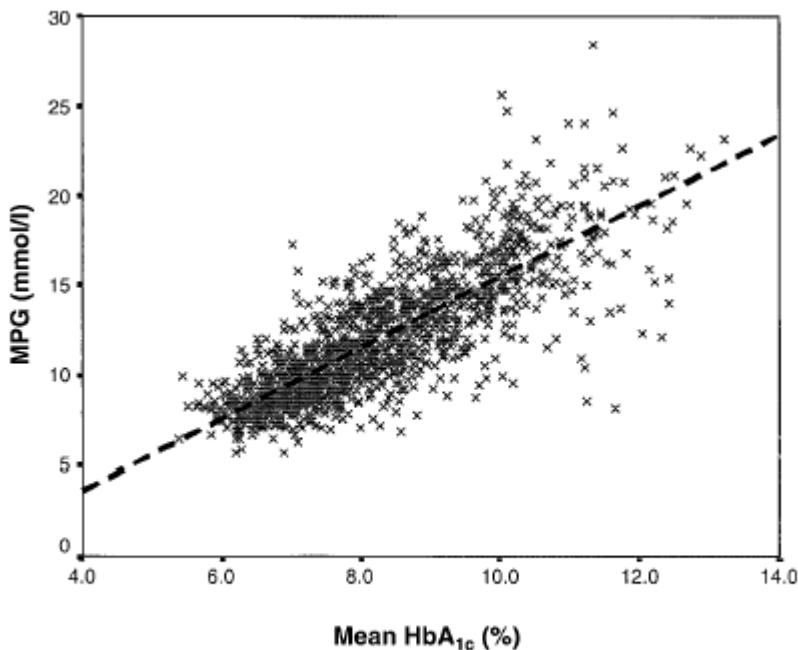
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**OBJECTIVE:**To define the relationship between HbA<sub>1c</sub> and plasma glucose (PG) levels in patients with type 1 diabetes using data from the Diabetes Control and Complications Trial (DCCT).

**RESEARCH DESIGN AND METHODS:** The DCCT was a multicenter, randomized clinical trial designed to compare intensive (three or more insulin injections daily or use of an insulin pump) and conventional (one or two insulin injections per day) therapies and their relative effects on the development and progression of diabetic complications in patients with type 1 diabetes. Quarterly HbA<sub>1c</sub> and corresponding seven-point capillary blood glucose profiles (premeal, postmeal, and bedtime) obtained in the DCCT were analyzed to define the relationship between HbA<sub>1c</sub> and PG. Only data from complete profiles with corresponding HbA<sub>1c</sub> were used (n = 26,056). Of the 1,441 subjects who participated in the study, 2 were excluded due to missing data. For each profile, the seven time points were connected by straight lines over time for a 24-hour period, and then the trapezoidal areas under each curve were determined, added together, and divided by time. Mean plasma glucose (MPG) was estimated by multiplying capillary blood glucose by 1.11. Linear regression analysis weighted by the number of observations per subject was used to correlate MPG and HbA(1c).

**RESULTS:** Linear regression analysis, using MPG and HbA<sub>1c</sub> summarized by patient (n = 1,439), produced a relationship of MPG (mmol/l) = (1.98 · HbA<sub>1c</sub>) - 4.29 or MPG (mg/dl) = (35.6 · HbA<sub>1c</sub>) - 77.3, r = 0.82)(Figure 1). Table 1 shows approximate MPG based on increments of 2 mmol/L or 35 mg/dL per 1% change in HbA<sub>1c</sub>. Among individual time points, afternoon and evening PG (postlunch, predinner, postdinner, and bedtime) showed higher correlations with HbA<sub>1c</sub> than the morning time points (prebreakfast, postbreakfast, and prelunch).

**CONCLUSIONS:** We have defined the relationship between HbA<sub>1c</sub> and PG as assessed in the DCCT. Knowing this relationship can help patients with diabetes and their healthcare providers set day-to-day targets for PG to achieve specific HbA<sub>1c</sub> goals. Fasting PG should be used with caution as a surrogate measure of MPG because it may significantly underestimate HbA<sub>1c</sub> levels.



**Figure 1**—MPG versus HbA<sub>1c</sub>: n = 1,439; r = 0.82; PG (mmol/l) = (1.98 · HbA<sub>1c</sub>) - 4.29. The dashed line indicates the regression line.

**Table 1**—MPG as estimated from the regression line and approximate MPG (based on MPG change of 35 mg/dl or 2 mmol/l per 1% change in HbA<sub>1c</sub>) at different HbA<sub>1c</sub> levels

HbA <sub>1c</sub> (%)	Regression- estimated MPG		Approximate MPG for clinical use	
	mmol/l	mg/dl	mmol/l	mg/dl
4	3.6	65	3.5	65
5	5.6	101	5.5	100
6	7.6	137	7.5	135
7	9.6	172	9.5	170
8	11.5	208	11.5	205
9	13.5	244	13.5	240
10	15.5	279	15.5	275
11	17.5	315	17.5	310
12	19.5	350	19.5	345

Rev Invest Clin. 2002 Nov-Dec;54(6):527-41.

## **Insulin analogues. A critical review.**

**Gomez-Perez FJ, Hernandez-Jimenez S, Aguilar-Salinas CA, Rull JA.**

Multiple and important technological innovations in the field of insulin therapy have appeared in the last decade. Insulin analogues with novel pharmacokinetics have been developed. The first of these analogues to appear in the market was insulin lispro. We believe that the most part of the studies carried out with this molecule in comparison with regular insulin were unfair as long as its short duration of action was ignored, since in many of these studies it was administered with meals and with only one dose of intermediate insulin given at night. Several studies done mainly by Italian investigators have proven this concept being true in studies with adequate baseline insulin coverage. Insulin aspart has appeared recently in the market in the United States with very similar effects to lispro. The FDA has recently approved a new ultralong acting analogue. The main advantages are its long, peakless action with better effects during down hours and a lower incidence of hypoglycaemia. We also review other approaches with novel insulin molecules attached to thyroxin or fatty acids in order to create a bridge for binding to plasmatic proteins. These molecules have longer effects and some of them more selective sites of action. Finally we included a brief review of other routes of insulin administration.

Clin Pharmacokinet. 2002;41(13):1043-57.

## **Clinical pharmacokinetics and pharmacodynamics of insulin lispro mixtures.**

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Rapid-acting insulin analogues such as insulin lispro and insulin aspart produce a more physiological profile of insulin activity than does conventional regular human insulin because of their unique pharmacokinetics. These insulin analogues are absorbed rapidly from the subcutaneous injection site, resulting in a better matching of the appearance of insulin in the circulation with nutrient absorption from the intestine. In addition, they are shorter-acting than regular human insulin, thus decreasing the risk of late postprandial hypoglycaemia due to inappropriate hyperinsulinaemia. Because self-prepared mixtures of these rapid-acting insulin analogues with longer-acting insulins such as neutral protamine Hagedorn (NPH) insulin have been shown to be clinically useful, and because manufactured fixed-ratio mixtures of regular human insulin and NPH already represent a large proportion of insulin use, manufactured fixed-ratio mixtures of insulin lispro and a sustained-release insulin known as NPL have been developed (insulin lispro mixtures). NPL is a protamine-based insulin lispro formulation with pharmacokinetics and glucodynamics comparable to those of human NPH insulin. NPL was developed for use within insulin lispro mixtures because an exchange between soluble insulin lispro and protamine-bound human insulin within human NPH precludes prolonged storage of mixtures of these insulins. An insulin lispro mixture consisting of 25% insulin lispro and 75% NPL is now commercially available. This preparation is intended primarily as an alternative to human insulin 30/70, which is commonly used within a twice-daily injection regimen. A mixture containing 50% insulin lispro and 50% NPL is also available. The rapid activity of insulin lispro is maintained within insulin lispro mixtures, allowing injection just prior to a meal, a convenience that is not available with commercial mixtures of regular human insulin and human NPH insulin, which should be injected 30 to 45 minutes prior to meals. As with insulin lispro itself, the rapid action of insulin lispro within the insulin lispro mixtures also results in a smaller increase in blood glucose levels after meals than with comparable human insulin mixtures. In addition, data from two studies have shown that when

Mix25 is injected prior to the evening meal the incidence of nocturnal hypoglycaemia is decreased in comparison with the same dose of human insulin 30/70. The combined rapid and prolonged insulin activity provided by insulin lispro mixtures has been defined both in healthy subjects without diabetes and in patients with diabetes.

Diabete Metab. 1991 Jan-Feb;17(1):49-54.

### **Premixed insulin at ratio 3/7 and regular + isophane insulins at mixing ratios from 2/8 to 4/6 achieve the same metabolic control.**

**Cucinotta D, Mannino D, Lasco A, Di Cesare E, Musolino C, Alessi R.**

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The insulin regimen with two daily injections is still that more frequently used. Often regular and NPH insulins are mixed at different ratios according to the patient's need; however, the mixture preparation can involve several errors. Efficacy, safety and compliance were evaluated comparing a premixture 3/7 (Actraphane HM) with extemporaneous mixtures of regular + NPH at mixing ratios ranging from 2/8 to 4/6, in a cross-over study of 8 weeks involving 20 insulin dependent diabetics. Metabolic control, hypoglycaemic episodes, insulin dose and proportions were similar with both treatments while a higher compliance was achieved with the premixture. In conclusion, premixture 3/7 and extemporaneous mixture (from 2/8 to 4/6) obtain the same efficacy and safety but the former shows a higher acceptability.

Diabetes Care. 1995 Jun;18(6):855-7.

### **A comparison of premixed insulin preparations in elderly patients. Efficacy of 70/30 and 50/50 human insulin mixtures.**

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**OBJECTIVE--**To compare the postprandial hyperglycemic response to a standard breakfast of two premixed humulin insulin mixtures, 50/50 (50% NPH human insulin and 50% regular human insulin) and 70/30 (70% NPH human insulin and 30% regular human insulin) in elderly non-insulin-dependent diabetes mellitus (NIDDM) patients. **RESEARCH DESIGN AND METHODS--**On two mornings, each patient (n = 20) consumed a standard breakfast after a single dose of 50/50 or 70/30 insulin (0.3 U/kg) was administered in a randomized crossover fashion. Plasma glucose and serum free insulin concentrations were measured before and for 4 h after insulin administration. **RESULTS--**Plasma glucose reached a peak at 60 min and a nadir at 240 min for both types of insulin. No differences in maximum and minimum glucose concentrations, time to maximum and minimum glucose concentrations, or areas under the curve were noted. Free insulin levels did not differ significantly. **CONCLUSIONS--**These results suggest that small changes in the composition of premixed insulin mixtures in NIDDM patients may not result in improved postprandial glycemic control.

### **Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients.**

Diabet Med. 2002 May;19(5):393-9 Erratum in: Diabet Med. 2002 Sep;19(9):797..

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**AIM:** To compare the efficacy and safety of premixed insulin aspart (30% free and 70% protamine-bound, BIAsp 30) with human insulin premix (BHI 30) used in a twice-daily injection regimen in people with Type 1 and Type 2 diabetes. **METHODS:** People with Type 1 and Type 2 diabetes (n = 294) using twice-daily insulin

were randomized to a 12-week open-label comparison of BIAsp 30 and BHI 30. Efficacy was assessed by analysis of variance of 12-week data, adjusted for baseline level. RESULTS: BIAsp 30 was as effective as BHI 30 based on the primary efficacy measure, HbA1c, mean difference -0.01 (90% confidence interval (CI) -0.14; 0.12) %Hb. Meal-time self-measured blood glucose increment averaged over the three main meals was significantly lower in the BIAsp 30 group than in the BHI 30 group (-0.68 (-1.20; -0.16) mmol/l;  $P < 0.02$ ). Significant improvements were observed after breakfast, before lunch, after dinner and at bedtime ( $P < 0.02$ -0.05), with blood glucose around 1.0 mmol/l lower in the BIAsp 30 group. The number of major hypoglycaemic episodes with BIAsp 30 was half that with BHI 30. However, the overall risk of both minor and major hypoglycaemia did not differ significantly between treatments. CONCLUSION: Post-prandial glycaemic control was significantly improved, without increasing the risk of hypoglycaemia, and overall control was similar when people with Type 1 and Type 2 diabetes were treated on a twice-daily regimen with immediate premeal injections of BIAsp 30 compared with BHI 30 but HbA1c was unchanged.