

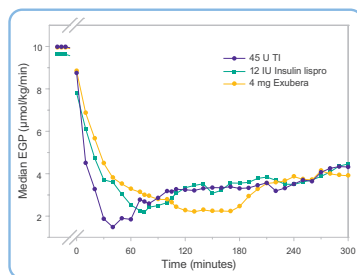
# Technosphere® Insulin Suppresses Endogenous Glucose Production Earlier Than a Rapid-Acting Analog (Lispro) and an Inhaled Insulin (Exubera)

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## ABSTRACT

**Background and aims:** Available insulins are unable to replicate normal hepatic glucose suppression, presumably due to slow absorption. Technosphere® Insulin (TI) is an ultra rapid-acting insulin generating peak insulin levels within 12 to 14 minutes of dosing. We conducted a study to determine whether the unique pharmacokinetic profile of TI resulted in a more rapid suppression of endogenous glucose production (EGP). **Materials and methods:** We compared 45 U TI administered by inhalation with 12 IU sc insulin lispro and 4 mg inhaled Exubera (EXB) in an open-label, single-dose, three-way crossover study incorporating a meal challenge (nutritional energy drink [12 fl oz] enriched with U13-C-glucose) in 18 insulin-treated subjects with type 2 diabetes and normal pulmonary function. A continuous glucose infusion enriched with 6,6-<sup>2</sup>H<sub>2</sub> glucose was used to assess EGP. Prior to the meal, subjects' blood glucose was adjusted to 90 mg/dL using an individualized continuous low-dose iv insulin infusion, which was fixed 90 minutes before dosing. If necessary, glucose was infused to maintain blood glucose at ≥ 90 mg/dL. **Results:** EGP suppression occurred markedly earlier following TI, followed by insulin lispro and EXB (40, 75, and 130 minutes postdose of the median EGP-time profiles, respectively). Significant differences between insulin lispro and EXB were observed up to 40 minutes compared with TI ( $p < 0.002$ ) and up to 2 hours for the EXB-TI comparison ( $p < 0.05$ ). Median total areas over the EGP curve were comparable across groups (1,938, 1,842, and 2,294 μmol/min). Median postprandial blood glucose AUCs were 53,343, 50,608, and 54,598 mg/dL\*min for TI, insulin lispro, and EXB, respectively. **Conclusion:** EGP was suppressed earlier following TI administration compared with sc insulin lispro and inhaled EXB, which suggests that treatment with TI may result in a more physiologic EGP suppression.



## BACKGROUND AND AIMS

The development of hyperglycemia results from an imbalance between systemic glucose delivery and glucose utilization. In type 2 diabetes (T2DM), hyperglycemia related to an increase in endogenous glucose production develops in the presence of normal or increased plasma insulin concentrations and is present in T2DM patients even with modest hyperglycemia.<sup>1</sup> The objective of this trial was to compare the effect of TI, insulin lispro, and EXB on EGP determined by a meal challenge test.

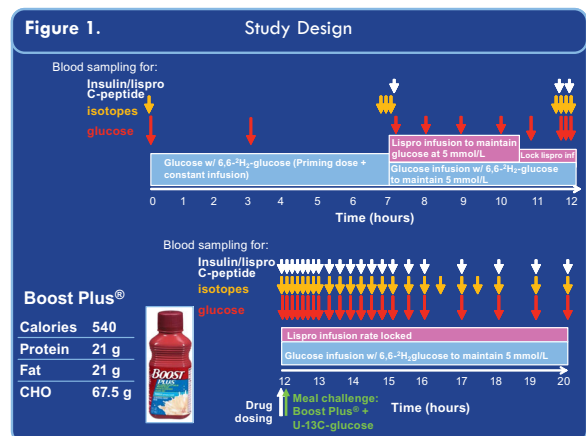
## MATERIALS AND METHODS

### Study Population

This was a randomized, open label, 3-way cross-over study in 18 nonsmoking, insulin-treated subjects with a clinical diagnosis of T2DM, currently on a stable anti-diabetic regimen that included insulin ≥ 3 months and an HbA1c ≤ 8.5%. The study was approved by the local ethics committee, and all subjects gave their written informed consent prior to starting the study.

### Study Procedures

In this study (see Figure 1), radio-labeled isotopes were used to distinguish between endogenous glucose production and exogenous glucose. At study start, 12 hours before dosing, subjects received an initial priming dose of 6 mg/kg of 6,6-<sup>2</sup>H<sub>2</sub> glucose, followed by a constant infusion of 6,6-<sup>2</sup>H<sub>2</sub> glucose for a 7-hour equilibration period to attain a steady-state tracer enrichment level. At 7 hours, the subjects received an individualized iv infusion of insulin lispro to suppress endogenous insulin secretion (fixed 90 minutes prior to dosing and continued until 480 minutes postdose), and a 20% glucose solution, enriched with



## MATERIALS AND METHODS (CONT'D)

8 mg of 6,6-<sup>2</sup>H<sub>2</sub> glucose per gram of glucose, to maintain a target blood glucose (BG) level of 90 mg/dL for at least 5 hours before dosing. Following an overnight fast, at each of the three treatment visits, each subject received a single dose of the test treatment immediately prior to consuming a nutritional energy drink (Boost Plus®) [12 fl oz] enriched with U13-C-glucose. The treatment periods were separated by a washout period of 7 to 21 days.

### Pharmacokinetic Analysis

Because the lispro treatment concentrations could not be analytically distinguished from the baseline lispro infusion, the sum of insulin lispro and regular human insulin concentrations were used for the PK analysis for all treatments. This allowed for a comparison of total insulin exposure across the three groups.

The following PK parameters were derived using noncompartmental analysis using WinNonlin v 5.2 (Pharsight Corporation, Mountain View, CA): observed peak insulin concentration ( $C_{max}$ ), time to peak insulin ( $t_{max}$ ), and insulin exposure as measured by the area under the insulin concentration-time curve from time 0 until  $t$  minutes postdose ( $AUC_{0-t}$ ), calculated by the linear-trapezoidal method.

### Pharmacodynamic Analysis

The total blood glucose and GIR values were used for the pharmacodynamic analysis and parameter calculation. The appearance rate of glucose originating from the meal ( $R_a$  meal) and EGP were estimated as described by Hovorka et al.<sup>2</sup> EGP areas over the curve (AOC) were calculated using the baseline corrected values, by subtracting the average of the values from at -20, -5, and 0 minutes from all postdose EGP values for each subject and treatment, with all positive results set to zero. For  $R_a$  meal, untransformed estimated values were used.

## RESULTS

### Study Population

Eighteen subjects were enrolled in the study. Summary demographics, other baseline characteristics are presented in Table 1.

Table 1. Demographics and Other Baseline Characteristics

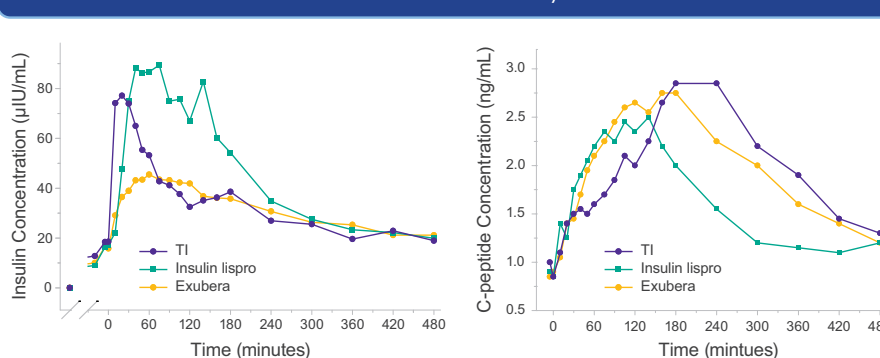
Demographic Characteristics	Category/Statistics	Value
Age (years)	Mean ± SD	55 ± 7
Gender (%)	Female	3 (17)
	Male	15 (83)
Race (%)	Caucasian	18 (100)
Weight (kg)	Mean ± SD	92 ± 12
Height (cm)	Mean ± SD	176 ± 8
BMI (kg/m <sup>2</sup> )	Mean ± SD	30 ± 3

### Insulin Pharmacokinetics

#### Insulin Concentrations

The median total insulin and C-peptide concentration-time profiles are shown in Figure 2.

Figure 2. Median Total Insulin (left panel) and C-peptide (right panel) Concentration-Time Profiles by Treatment



## RESULTS (CONT'D)

### Pharmacokinetic Parameters

The ratios of the extent of exposure, as determined by total insulin  $AUC_{0-tlast}$  for TI: Exubera: insulin lispro were 1: 0.98: 1.39. Overall exposure 39% higher in the insulin lispro group than in the TI group, and 41% higher than in the Exubera group. Insulin pharmacokinetic parameters are presented in Table 2.

Table 2. Summary Statistics of Total Insulin Pharmacokinetic Parameters

Treatment		$t_{max}$ (min)	$C_{max}$ (μU/mL)	$AUC_{0-180}$ (μU/mL-min)	$AUC_{0-300}$ (μU/mL-min)	$AUC_{0-tlast}$ (μU/mL-min)
TI	Mean	86	86	8431	12138	15988
	Median	20	83	8626	12037	15744
	CV%	44	44	42	47	50
Insulin lispro	Mean	95	95	12502	17528	22207
	Median	75	96	12363	17474	21436
	CV%	32	37	39	42	42
Exubera	Mean	56	56	7733	11854	15748
	Median	98	51	6818	10653	15063
	CV%	47	52	52	54	54

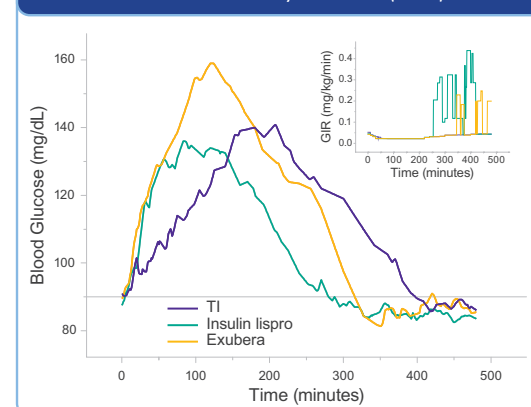
\*Five patients had last insulin concentrations that were <480 minutes; none was shorter than 300 minutes.

### Insulin Pharmacodynamics

#### Blood Glucose Concentrations and GIR

Median blood glucose concentration-time and GIR-time profiles are presented in Figure 3. Due to the quick rise in insulin levels following TI administration, blood glucose levels were better controlled early following TI administration. Much larger glucose infusions were needed to maintain BG at 90 mg/dL following Exubera and insulin lispro in the latter part of the treatment period when compared to TI, with 10 and 14 subjects receiving additional glucose infusions late in the profile in the Exubera and insulin lispro groups, respectively, compared to 5 subjects in the TI group. In the TI group, 5 out of 18 subjects required some glucose infusion within the first hour postdose, versus 2 subjects in the insulin lispro group and 0 subjects treated with Exubera.

Figure 3. Blood Glucose Concentration-Time Profiles by Treatment (main panel); GIR-Time Profiles by Treatment (insert)



#### Glucose Appearance Rate

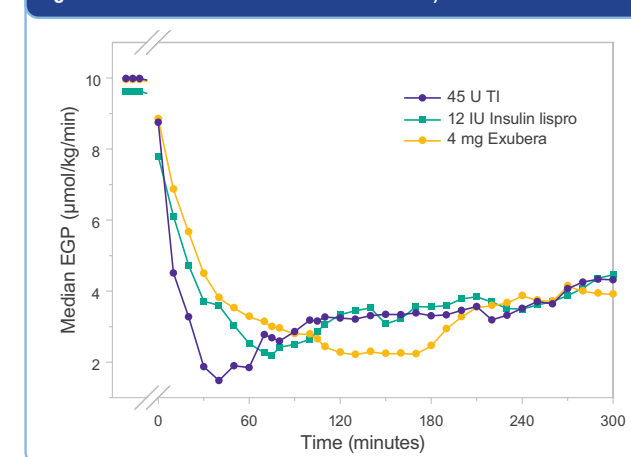
The absorption rate-time profiles are shown in Figure 4. Following Boost Plus® ingestion, subjects in all three treatment groups had similar absorption rate profiles, returning to baseline values at approximately 300 minutes post-meal.

#### Endogenous Glucose Production

Endogenous glucose production was suppressed earlier in the TI group when compared to the insulin lispro and Exubera groups. All three treatments suppress EGP. The maximum EGP suppression was comparable across treatments (Figure 5).

## RESULTS (CONT'D)

Figure 5. Median EGP-Time Profiles by Treatment



### Statistical Analysis of Incremental EGP AOC

After the percent of the EGP  $AOC_{0-300}$  was calculated at each nominal time point, one-way ANOVA analyses were carried out. Two group comparisons were conducted at each time point, with Dunnett's  $t$  test, using TI as the control. Significant differences between both insulin lispro and Exubera were observed up to 40 minutes when compared to TI ( $p < 0.002$ ), and up to 2 hours for the Exubera-TI comparison ( $p < 0.05$ ) (Table 3).

Table 3. Summary Statistics of EGP AOC

Group		$AOC_{0-30}$ (μmol/kg)	$AOC_{0-60}$ (μmol/kg)	$AOC_{0-180}$ (μmol/kg)	$AOC_{0-300}$ (μmol/kg)
TI	Mean	97	267	841	1343
	Median	93	285	940	1564
	CV%	70	63	55	53
Insulin lispro	Mean	61	199	802	1287
	Median	56	190	851	1289
	CV%	61	58	49	49
Exubera	Mean	63	210	986	1663
	Median	60	209	1035	1687
	CV%	50	41	33	34

## CONCLUSIONS

Following administration of 45 U TI and 4 mg Exubera, relative insulin exposure was approximately 61% and 59% when compared to insulin lispro, for the TI and Exubera treatments, respectively. Following a nutritional energy drink (Boost Plus®) [12 fl oz], blood glucose profiles peaked earlier for both the insulin lispro and Exubera treatments when compared to the TI treatment.

EGP was suppressed earlier following TI administration compared to sc insulin lispro and inhaled Exubera. The extent of EGP suppression was comparable for all three treatments in the postmeal period, however, a greater proportion of EGP occurred with TI within the first hour after dosing. Significant differences between both insulin lispro and Exubera were observed up to 40 minutes when compared to TI ( $p < 0.002$ ), and up to 2 hours for the Exubera-TI comparison ( $p < 0.05$ ). This finding may be attributed to TI's unique pharmacokinetic profile, and suggests that the ultra-rapid rise in insulin concentrations following TI administration has a more rapid effect on the liver, resulting in a more physiologic EGP suppression.

## ACKNOWLEDGEMENTS

This study was conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany.

## REFERENCES

- Perriello G, et al. Evidence of increased systemic glucose production and gluconeogenesis in an early stage of NIDDM. *Diabetes*. 1997;46(6):010-6.
- Hovorka R, et al. Calculating glucose fluxes during meal tolerance test: a new computational approach. *Am J Physiol Endocrinol Metab*. 2007;293(2):E610-9.