Comparison of Insulin Aspart and Lispro

Pharmacokinetic and metabolic effects

CAROL HOMKO, RN, PHD
ANTONIO DELUZIO, DO
CAROLYN JIMENEZ, PHD
JERZY W. KOLACZYNSKI, MD, PHD
GUENTHER BODEN, MD

OBJECTIVE — To compare insulin levels and actions 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 (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 (9.4 ± 1.9 U) in random order. For the next 4–5 h, their plasma glucose was clamped at ~5.5 mmol/l with a variable infusion of 20% glucose. The study was terminated after 8 h.

RESULTS — Both insulin analogs produced similar serum insulin levels (250–300 pmol/l) at ~30 min and disappeared from serum after ~4 h. 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 ~2–3 h and disappeared after ~5–6 h. Effects on lipid metabolism (plasma free fatty acid, ketone body levels, and free fatty acid oxidation) appeared to peak earlier (at ~2 h) and disappeared earlier (after ~4 h) than the effects on carbohydrate metabolism.

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.

Diabetes Care 26:2027–2031, 2003

Two rapidly acting insulin analogs, insulin lispro and aspart, are currently available in the U.S. and other countries for use in the management of diabetes. Insulin lispro differs from human insulin by the substitution of proline with lysine in position 28 and lysine with proline in position 29 of the B chain; insulin aspart differs from human insulin by a single substitution of proline with aspartic acid in position B28. These changes reduce the tendency of the analogs to self-associate into dimers and hexamers and, thus, increase the rate of absorption into the blood after subcutaneous injection. This results in faster peak insulin concentration than is found with regular human insulin, in better postprandial glucose control, and less frequent late hypoglycemia (1–4). Therefore, the two rapidly acting insulin analogs are increasingly being used in clinical practice. However, it remains uncertain whether they are completely interchangeable or whether they differ in some or all of their actions.

The purpose of this study was, therefore, to compare blood insulin levels and actions on glucose and fat metabolism after subcutaneous injection of insulin lispro and aspart in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

We studied seven patients with type 1 diabetes (five women and two men). The subjects' age, weight, height, and body composition are shown in Table 1. At the time of study, the diabetic patients were free of detectable diabetic complications. They had no other disease apart from diabetes and were not taking any medications other than insulin. Five patients used insulin pumps and two used multiple daily insulin injections. All patients were receiving lispro insulin before the study. The women were studied in the follicular phase of their menstrual cycle.

Table 1—*Clinical features of patients studied*

	Mean (range)
Sex (M/F)	2/5
Age (years)	24 (19–37)
Height (cm)	171 (169–182)
Weight (kg)	72.3 (58–89)
Percent fat	27.7 (11–40)
BMI (kg/m^2)	24.9 (21–28)
Duration of diabetes (years)	8.2 (0.5–13)
Insulin analog dose received during study (units)	9.4 (2–15)
HbA_{1c} (%)*	7.6 (5.7–9.3)

*Reference range 4.3–5.7%.

From the General Clinical Research Center and Division of Endocrinology/Diabetes/Metabolism, Temple University School of Medicine, Philadelphia, Pennsylvania.

Address correspondence and reprint requests to Guenther Boden, Temple University Hospital, 3401 N. Broad St., Philadelphia, PA 19140. E-mail: bodengh@tuhs.temple.edu.

Received for publication 23 October 2002 and accepted in revised form 20 February 2003.

C.H. is on the Educators' Advisory Boards of the TheraSense Corporation, a manufacturer of blood glucose meters, and Amylin Pharmaceuticals, Inc., a manufacturer of pharmaceuticals related to the treatment of diabetes, and has received honoraria for speaking engagements from Aventis Pharmaceuticals and Disetronic Medical Systems, Inc. G.B. is an advisory panel member for Novo Nordisk, GlaxoSmithKline, and Aventis and has received honoraria for speaking engagements from Novo Nordisk, GlaxoSmithKline, Aventis, and Lilly.

Abbreviations: EGP, endogenous glucose production; FFA, free fatty acid; GIR, glucose infusion rate; G_{Ra}, rate of glucose appearance; G_{Rd}, rate of glucose disappearance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Informed written consent was obtained from all subjects after explanation of the nature, purpose, and potential risks of the study. The study protocol was approved by the Institutional Review Board of Temple University Hospital.

Study design

All subjects were admitted to the General Clinical Research Center at Temple University Hospital the day before the studies. Their evening dose of insulin was withheld. At 6:00 P.M. they were fed a standard meal consisting of 53% carbohydrate, 15% protein, and 32% fat. After that, they fasted for the duration of the study but were allowed water ad libitum.

During the night, their blood glucose concentration was maintained between 5.5 and 6.7 mmol/l with an intravenous infusion of regular insulin. The insulin infusion was discontinued at ~7:00 A.M. the following day. At ~6:00 A.M. an infusion of [6,6-$^2H_2$]glucose was started and continued until the end of the study. At ~8:00 A.M. they received a subcutaneous injection into the abdominal wall of a rapidly acting insulin analog (either aspart or lispro) at a dose equal to one-half of their normal daytime insulin dose. All subjects received both insulins, 1 month apart, in random order. The patients, the nurses who collected the blood, and the technician who analyzed the blood were all unaware as to which analog was given.

After injection of the insulin analogs, plasma glucose levels were kept at ~5.5 mmol/l with a variable infusion of 20% dextrose in water (5). Eight hours after insulin injection, the study was terminated; the patients restarted on their normal insulin regimen, were fed a meal, and were discharged from the hospital.

Glucose turnover

Glucose turnover was determined using the stable isotope [6,6-$^2H_2$]glucose as described (6). To assure isotope equilibration, the tracer infusion was started 120 min before initiation of the clamp starting with a bolus of 30 μmol, followed by a continuous infusion of 0.3 μmol · kg^{-1} · min^{-1}. Blood was collected at 30- to 60-min intervals (−120, −30, 0, 30, 60, 120, 180, 240, 300, 360, 420, and 480 min) for determination of isotope enrichment. Rates of glucose appearance (G_{Ra}) and disappearance (G_{Rd}) were calculated from the isotope enrichments before (−30 to 0 min) and during the 8-h study

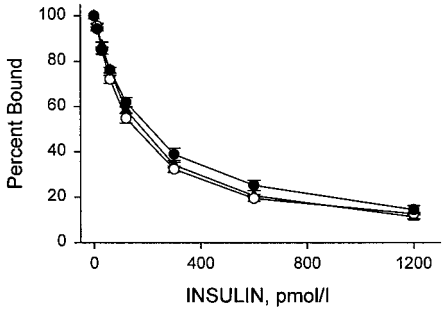

Figure 1—*Displacement of ^{125}I-labeled human insulin from human anti-insulin serum by human insulin (regular, ▲), insulin lispro (○), and insulin aspart (●) (n = 6).*

using Steele's equation for nonsteady state (7). Underestimation of G_{Ra} during hyperinsulinemia was avoided by adding [6,6-$^2H_2$]glucose (6.9 mmol/100 ml) to the unlabeled glucose infused to maintain euglycemia.

Endogenous glucose production

Endogenous glucose production (EGP) was calculated as the difference between the isotopically determined G_{Ra} and the glucose infusion rates (GIR) needed to maintain stable blood glucose levels during insulin infusion (EGP = G_{Ra} − GIR).

Indirect calorimetry

Respiratory gas exchange rates were determined at 30- to 60-min intervals with a metabolic measurement cart as previously described (8). Rates of protein oxidation were estimated from the urinary nitrogen excretion after correction for changes in urea nitrogen pool size (9). Rates of protein oxidation were used to determine the nonprotein respiratory quotient. Rates of fat oxidation were determined with the tables of Lusk, which are based on anonprotein respiratory quotient of 0.707 for 100% oxidation and 1.00 for 100% carbohydrate oxidation.

Body composition

Body composition was determined by bioimpedance analysis (10).

Analytical procedures

Plasma glucose was measured with a glucose analyzer with the glucose oxidase method every 15–20 min. Free insulin levels were determined in deproteinized serum by radioimmunoassay with a specific antibody that cross-reacts only minimally (<0.2%) with proinsulin (Linco,

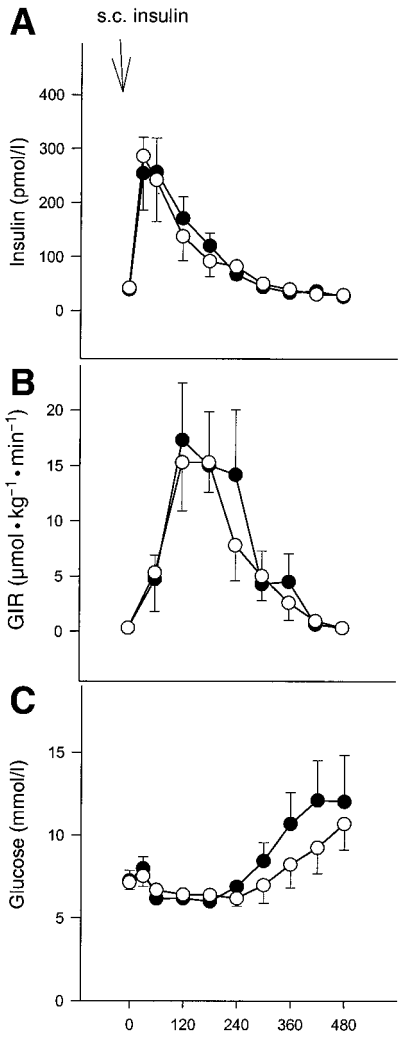

Figure 2—A: *Serum insulin levels before and after subcutaneous injection (at 0 min) of insulin aspart (●) or insulin lispro (○) in seven patients with type 1 diabetes. Data are means ± SEM.* B: *GIR needed to prevent hypoglycemia in the same seven patients.* C: *Plasma glucose concentrations before and after subcutaneous injection of insulin aspart or insulin lispro in the same seven patients.*

St. Charles, MO). This antiserum recognizes equally human insulin, insulin lispro, and aspart (Fig. 1). Plasma fatty acids were determined enzymatically in chilled plasma with a kit (Wako, Richmond, VA). C-peptide was determined by radioimmunoassay (Linco). Plasma β-hydroxybutyrate and acetoacetate were determined enzymatically.

Statistical analysis

All data are expressed as means ± SEM. Statistical significance was assessed using two-way repeated measures ANOVA and

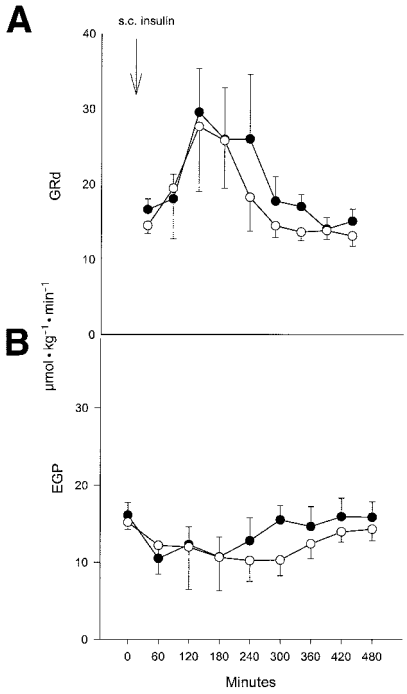

Figure 3—*Rates of isotopically determined G_{Rd} (A) and EGP (B) before and after subcutaneous injection (at 0 min) of either insulin aspart (●) or insulin lispro (○) in seven patients with type 1 diabetes.*

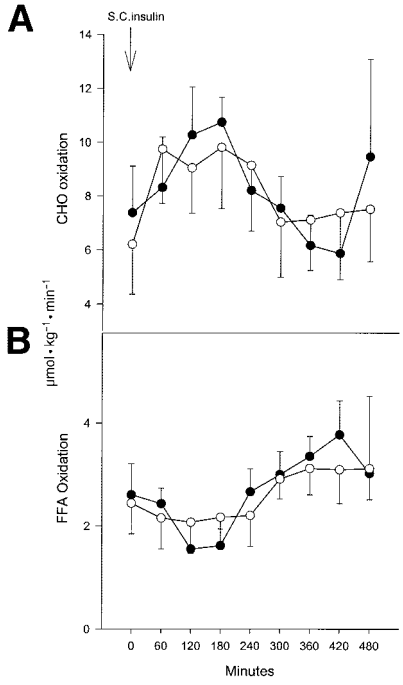

Figure 4—*Rates of carbohydrate (A) and FFA oxidation (B) before and after subcutaneous injection (at 0 min) of either insulin aspart (●) or insulin lispro (○) in seven patients with type 1 diabetes.*

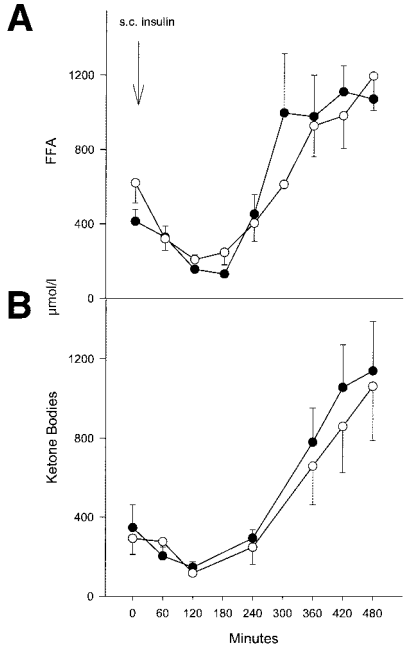

Figure 5—*Plasma levels of FFA (A) and total ketone bodies (β-hydroxybutyrate plus acetoacetate, B) before and after subcutaneous injection (at 0 min) of either insulin aspart (●) or insulin lispro (○) in seven patients with type 1 diabetes.*

two-tailed Student's *t* test. A $P < 0.05$ was considered significant.

RESULTS

Insulin levels

Insulin concentrations rose from 39 ± 6 to 256 ± 63 pmol/l 30 min after injection of insulin aspart and from 43 ± 10 to 286 ± 99 pmol/l 30 min after injection of insulin lispro ($P = 0.24$). After that, insulin levels declined at similar rates in both groups reaching basal levels ~4 h after injection (Fig. 2).

GIR

GIR reached 17.3 ± 5.2 and 15.3 ± 4.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ 120 min after injection of insulin aspart and lispro, respectively ($P = 0.61$) (Fig. 2). After that, GIR decreased in both groups, reaching levels not different from 0 at ~300 min.

Plasma glucose

Preinjection glucose concentrations were 7.3 ± 0.6 and 7.2 ± 0.4 mmol/l ($P = 0.68$), respectively, in the insulin aspart and insulin lispro groups. After injection of the insulin analogs, blood glucose was prevented from falling for ~300 min by infusion of exogenous glucose. After that, glucose levels rose, reaching 12.1 ± 2.8 and 10.7 ± 1.6 mmol/l ($P = 0.67$), respectively, in the insulin aspart and lispro groups at the end of the study (Fig. 2).

G_{Rd}

G_{Rd} rose from 16.6 ± 1.4 to 26.8 ± 6.6 and from 14.5 ± 1.1 to 27.6 ± 8.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, respectively, at ~120 min in the insulin aspart and lispro groups. G_{Rd} then declined in both groups, reaching basal levels after ~240 min. There were no statistically significant differences between the two groups at any time ($P = 0.61$) (Fig. 3).

EGP

In response to insulin injections, EGP decreased from 16.1 ± 1.7 to 9.6 ± 3.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and from 15.2 ± 0.9 to 11.5 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at 240 min, respectively, in the insulin aspart and insulin lispro groups. The differences were not statistically significant ($P = 0.86$) (Fig. 3).

Carbohydrate and free fatty acid oxidation

Basal carbohydrate oxidation rates were similar in both groups. They increased comparably after analog injection until ~3 h and then declined. Carbohydrate oxidation rates in both groups were not statistically significant from each other at any time during the studies ($P = 0.69$). Similarly, free fatty acid (FFA) oxidation rates first decreased and then increased. There were no statistically significant differences between the two groups ($P = 0.22$) (Fig. 4).

Plasma FFA and ketone bodies

Basal plasma FFA levels decreased from 413 ± 65 to 130 ± 19 and from 620 ± 109 to 207 ± 40 µmol/l, 180 and 120 min, respectively, after injection of insulin aspart and insulin lispro. After that, FFA levels rose in both groups reaching 1,071 ± 112 and 1,195 ± 185 µmol/l after 480 min. The differences between the groups were not statistically significant ($P = 0.40$). Ketone body concentrations changed in parallel with FFA concentrations. Again, there were no significant differences between the two groups at any time ($P = 0.70$) (Fig. 5).

C-peptide and glucagon

Preinjection levels of C-peptide (0.07 ± 0.04 and 0.08 ± 0.04 nmol/l, $P = 0.71$) and glucagon (49 ± 5 and 46 ± 6 pg/ml, $P = 0.82$) for the aspart and lispro groups, respectively, did not change significantly throughout the studies.

CONCLUSIONS

Comparison of insulin levels

After subcutaneous injection of an equal amount of either insulin lispro or aspart into the same patients, free insulin reached similar concentrations (~250–300 pmol/l) at approximately the same time (30–60 min postinjection), and after that free insulin disappeared from serum at comparable rates, reaching preinjection levels at ~240 min.

Insulin analog concentrations were measured with an anti-insulin antibody that bound insulin, insulin lispro, and aspart with equal affinity over the range of insulin levels observed in this study. Therefore, serum levels of these three insulins could be directly compared with each other.

A limitation of our study was that blood was sampled only every 30–60 min. This precluded precise definition of peak insulin levels, the time to reach peak levels, and the time of disappearance of injected insulin from the blood. Nevertheless, these limitations do not detract from the observation that both insulins produced virtually superimposable insulin concentration curves.

The results of the current study are similar to those of two other studies in which the pharmacokinetics of the two insulin analogs were compared (11,12). One study used a single blind, random crossover design in seven patients with type 1 diabetes and 5- to 10-min blood sampling during the first hour after injection. They reported that after subcutaneous injection of 10 units of either analog, plasma profiles resembled each other but lispro showed a slightly more rapid uptake and peaked and declined marginally faster. A second study, which appeared while our study was under review, showed complete equivalence of lispro and aspart with respect to pharmacokinetics profiles and effectiveness controlling postprandial glucose excursions (12).

Comparison of insulin actions

To our knowledge, this is the first study comparing action of lispro and aspart on carbohydrate and fat metabolism in the same patients. We found no significant differences comparing the actions of both analogs on G_{Rd} (>80% of which occurs in skeletal muscle [13]), on EGP (>80% of which occurs in the liver [14]), on GIR (reflecting a combination of insulin action on muscle and liver), and on carbohydrate oxidation. All of these effects peaked at ~2–3 h and had disappeared after ~5–6 h. As shown in Fig. 3, the nonsignificant differences in G_{Rd} and EGP were in opposite directions (i.e., insulin aspart was more active promoting glucose uptake but less active suppressing EGP). This supports the notion that the bioactivity profiles of the two insulins are interchangeable.

Similarly, there were no significant differences comparing actions of the two analogs on plasma FFA and ketone body levels nor on FFA oxidation. (Changes in plasma FFA levels closely reflect insulin action on lipolysis and is a very sensitive indicator of insulin action [15].) Insulin effects peaked at ~2 h and had disappeared after ~4 h. These results are in accord with previously published data on effects of insulin lispro (16,17) and insulin aspart (18–20).

Thus, the actions of both insulin analogs on carbohydrate and on lipid metabolism appeared to be indistinguishable from each other. This was not surprising in view of the similarity of their blood levels. Because of the small number of patients studied, we cannot completely rule out the possibly of small differences in some of the action of these two insulin analogs. Nevertheless, our data suggested that these two rapidly acting insulin analogs should be equally effective in treating the metabolic abnormalities of patients with type 1 diabetes.

Acknowledgments— This work was supported by National Institutes of Health Grants R01-AG-15363 (to G.B.), R01-DK-58895 (to G.B.), M01-RR-00349 (General Clinical Research Center Branch of the National Center for Research Resources), a Mentor Based Training Grant from the American Diabetes Association (to G.B.), and a Grant-in-Aid from Novo Nordisk Pharmaceuticals, Princeton, NJ.

We thank the nurses of the General Clinical Research Center for help with the studies and for excellent patient care, Karen Kresge and Maria Mozzoli for outstanding technical assistance, and Constance Harris Crews for typing the manuscript.

Information from this article has previously appeared in abstract form and was presented as a poster at the American Diabetes Association Annual Meeting, New Orleans, Louisiana, 13–17 June 2003.

References

1. Home PD, Lindholm A, Hylleberg B, Round P: Improved glycemic control with insulin aspart. *Diabetes Care* 21:1904–1909, 1998
2. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L: Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23: 583–588, 2000
3. Feinglos Thacker CH, English J, Bethel MA, Lane JD: Modification of postprandial hyperglycemia with insulin lispro improves glucose control in patients with type 2 diabetes. *Diabetes Care* 20:1539–1542, 1997
4. Anderson JH Jr, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, DiMarchi R: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment: Multicenter Insulin Lispro Study Group. *Diabetes* 46:265–270, 1997
5. Boden G, DeSantis R, Chen X, Morris M, Badoza F: Glucose metabolism and leg blood flow after pancreas/kidney transplantation. *J Clin Endocrinol Metab* 76: 1229–1233, 1993
6. Wolfe RR: Tracers in metabolic research. In *Radioisotope and Stable Isotope/Mass Spectrometry Methods*. New York, Alan R. Liss, 1984, p. 261
7. Steele R, Wall JS, DeBodo RC, Altszuler N: Measurement of size and turnover rate of body glucose pool by the isotope dilution method. *Am J Physiol* 187:15–24, 1956
8. Owen OE, Trapp VE, Reichard GA Jr, Mozzoli MA, Smith R, Boden G: Effects of therapy of the nature and quantity of fuels oxidized during diabetic ketoacidosis. *Diabetes* 29:365–372, 1980
9. Tappy L, Owen OE, Boden G: Effect of hyperinsulinemia on urea pool size and substrate oxidation rates. *Diabetes* 37: 1212–1216, 1988
10. Lukaski HC: Methods for the assessment of human body composition: traditional and new. *Am J Clin Nutr* 46:537–556, 1997
11. Hedman CA, Lindstrom T, Arnqvist HJ: Direct comparison of insulin lispro and aspart shows small differences in plasma insulin profiles after subcutaneous injec-

tion in type 1 diabetes. *Diabetes Care* 24: 1120–1121, 2001
12. Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, Hirschberger S, Peiber TR: A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25: 2053–2057, 2002
13. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J: Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest* 76:149–155, 1985
14. Stumvoll M, Chintalapudi U, Perriello G, Welle S, Gutierrez O, Gerich J: Uptake and release of glucose by the human kidney: postabsorptive rates and responses to epinephrine. *J Clin Invest* 96:2528–2533, 1995
15. Bondonna RC, Groop LC, Zych K, Shank M, DeFronzo RA: Dose-dependent effect of insulin on plasma free fatty acid turnover and oxidation in humans. *Am J Physiol* 259:E736–E750, 1990
16. Torlone E, Pampanelli S, Lalli C, Del Sindaco P, DiVincenzo A, Rambotti AM, Modarelli F, Epifano L, Kassi G, Perriello G, Brunetti P, Bolli G: Effects of the short-acting insulin analog [Lys(B28), Pro (B29)] on postprandial blood glucose control in IDDM. *Diabetes Care* 19:945–952, 1996
17. Jacobs MAJM, Keulen ETP, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine RJ: Metabolic efficacy of preprandial administration of Lys (B28), Pro (B29) human insulin analog in IDDM patients. *Diabetes Care* 20:1279–1289, 1997
18. Home PD, Barriocanal L, Lindholm A: Comparative pharmacokinetics and pharmacodynamics of the novel rapid-acting insulin analogue, insulin aspart, in health individuals. *Eur J Clin Pharmacol* 55:199–203, 1999
19. Home P, Lindholm A, Riis A: Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 17:762–770, 2000
20. Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, Madsbad S: Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. *Acta Diabetol* 37:41–46, 2000