Insulin Analog Lispro Decreases Insulin Resistance and Improves Glycemic Control in an Obese Patient With Insulin-Requiring Type 2 Diabetes

Subcutaneous insulin resistance is a rare but potentially severe phenomenon that may be due to insulin inactivation by dermal tissue (1). The insulin analog lispro (Humalog; Eli Lilly, Kyrtwal, The Netherlands) is more rapidly absorbed than regular insulin and may escape the proteolysis degradation by subcutaneous tissue. We report the case of an obese female patient with insulin-requiring type 2 diabetes in whom lispro administration led to improved metabolic control and markedly reduced daily insulin requirements.

Our patient was a 61-year-old obese woman (104 kg, BMI 40.1 kg/m^2) with type 2 diabetes since 35 years of age who had been treated with high doses of insulin (1.0 to 1.4 U · kg^{-1} · day^{-1}) for the past 15 years; she presented severe macrovascular complications (coronaropathy with unstable angina, carotid stenosis) associated with essential hypertension and combined dyslipidemia. Glycemic control was poor (HbA_{1c} 9.4%, reference range 4.5–6.5) in spite of three daily insulin injections, regular insulin (Actrapid HM; Novo Nordisk, Boulogne-Billancourt, France) before breakfast (34–40 U) and lunch (34–40 U) and regular plus NPH insulin (Mixtard 30 HM; Novo Nordisk) before dinner (60 U). No evident factor known to induce diabetic decompensation was found, and she had no circulating human insulin antibodies. To improve metabolic control, she followed several therapeutic trials in association with a 1,200-kcal diet. Neither metformin nor acarbose were used because of cardiac insufficiency and digestive intolerance, respectively. We first gave regular human insulin (Velosuline; Novo Nordisk) by means of a subcutaneous infusion (CSII) with a pump over 7 days, but glycemic control remained poor (mean premeal glycemia 14.4 mmol/l, mean 2-h postmeal glycemia 14.8 mmol/l), while daily insulin dose progressively increased from 160 to 340 U/day. A 72-h intravenous insulin administration (Actrapid HM) allowed the attainment of a better metabolic control (mean glycemia 8.5 mmol/l) with a significant reduction in the total amount of insulin required (220 U/day). At that time, we resumed the CSII treatment with regular human insulin for 1 week, but unfortunately, glycemic values increased again (mean premeal glycemia 12.2 mmol/l, mean 2-h postmeal glycemia 13.2 mmol/l), in spite of a progressive increase in insulin dose (from 320 to 420 U/day). Intravenous insulin administration for 3 days led this time again to an improved glycemic control (mean glycemia 9.9 mmol/l), with slightly less insulin (280 U/day). We decided then to initiate a CSII treatment with insulin analog lispro (Humalog), and we observed a significant and persistent metabolic improvement (mean premeal glycemia 7.3 mmol/l, mean 2-h postmeal glycemia 8.4 mmol/l), associated with a rapid decline in daily insulin requirements (from 320 to 160 U/day over 7 days). There was a slight weight reduction during the stay (from 104 to 102 kg).

In this patient, an improvement of glycemic control and a reduction of daily insulin doses was obtained with intravenous infusion of regular insulin and subcutaneous administration of insulin analog lispro, suggesting that her insulin resistance is mediated by dermal insulin inactivation. The observed metabolic improvement with insulin lispro was not related to the reduction of glucotoxicity, since the replacement of intravenous insulin infusion by CSII with regular insulin after 72 h of good glycemic control failed, compared with the use of CSII with lispro under the same conditions. Therefore, we believe that the metabolic improvement is related to a better subcutaneous absorption and diffusion of insulin lispro. A similar observation was reported in a 38-year-old woman with type 1 diabetes and apparent subcutaneous insulin resistance in whom CSII treatment with insulin lispro decreased HbA_{1c} levels from 14.2 to 10.9% and reduced the total daily insulin dose by 53% after 6 months (2); in this patient, subcutaneous injection of insulin lispro before a test meal was followed by a larger increase of serum insulin levels and a greater decrease of the 3-h glycemia than those observed after injection of regular insulin. Insulin lispro has also been effective in reducing insulin resistance due to high levels of insulin antibodies (3,4). A prolonged treatment with insulin lispro may also increase the amount and affinity of insulin receptors in obese patients with insulin-requiring type 2 diabetes (5).

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References

1. Schade DS, Duckworth WC: In search of the subcutaneous insulin resistance syndrome. *N Engl J Med* 315:147–153, 1986
2. Henrichs HR, Unger H, Trautman ME, Pfützner A: Severe insulin resistance treated with insulin lispro (Letter). *Lancet* 348:1248, 1996
3. Lahtela JT, Knip M, Paul R, Antonen J, Salmi J: Severe antibody-mediated human insulin resistance: successful treatment with the insulin analog lispro: a case report. *Diabetes Care* 20:71–73, 1997
4. Braimon J, O'Brien M, Kaulbach H, Moses A: The insulin analog lispro effectively treats anti-insulin antibody mediated insulin resistance (Abstract). *Diabetes* 45 (Suppl. 2):185A, 1996
5. Jehle RP, Fussganger RD, Seibold A, Luttke B: Pharmacodynamics of insulin lispro in 2 patients with type 2 diabetes mellitus. *Int J Clin Pharmacol Therap* 34:498–503, 1996

Type 2 Diabetes in Adults With Pseudopseudohypoparathyroidism

Case report

Albright's hereditary osteodystrophy (AHO) is an autosomal dominant disorder with characteristics of abnormal skeletal phenotype, such as short stature, obesity, round face, brachydactyly, and mental retardation. Patients with AHO can appear with either pseudohypoparathyroidism (PHP), which is due to parathyroid hormone resistance, or with pseudopseudohypoparathyroidism (pseudo-PHP), which involves no hormone resistance.