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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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.

These two conditions are considered variants of the same defect of the stimulatory guanine nucleotide-binding (Gs) protein of adenylate cyclase, which is necessary for parathyroid hormone and other hormones such as gonadotropin, beta-adrenergic agonist, and thyrotropin to use cAMP as an intracellular second messenger.

We described two related women with apparent AHO and late-onset diabetes. Both patients had normal serum calcium levels, normal parathyroid hormone levels, and the characteristic somatic features of short stature, round face, obesity, and shortened fourth and fifth metacarpals and metatarsals, consistent with pseudo-PHP.

Both disorders, PHP and pseudo-PHP, can occur within the same family, and there is accumulating evidence that genomic imprinting is involved in the disease (1). Full phenotypic expression (AHO and parathyroid hormone resistance, as in PHP type Ia) occurs in maternally transmitted cases, whereas partial expression (AHO without parathyroid hormone resistance, as in pseudo-PHP) occurs when the gene is paternally transmitted. The pedigree of our patients showed genetic transmission from their father.

Patients with type 2 diabetes have defects in insulin action, abnormal insulin secretion, and increased hepatic glucose production. Although precise pathways responsible for these defects have not been thoroughly identified, they are likely to be genetically heterogenous with mutations in several different genes that are able to cause hyperglycemia. Some reported genetic loci for type 2 diabetes have been mapped on chromosome 20q, chromosome 7p, chromosome 12q, chromosome 2, and so forth (2,3).

In most cases of AHO, reduced levels of Gs protein α subunit (Gsα protein) have been found. A number of deactivating mutations in the gene for Gsα protein located on chromosome 20q13 have been described for this disorder (1), but del(2)(q37) has also been described in some AHO patients (4) and thus explains the heterogeneity observed in this AHO disorder.

PHP type Ia or pseudo-PHP is assumed to be a Gsα protein problem and this protein is encoded by chromosome 20q13. 2–3. Occasionally, these disorders may be associated with resistance of diverse target tissues to hormones and neurotransmitters whose actions require stimulation of adenylate cyclase and thus open calcium channels. It should be considered whether this Gsα protein problem will lead to diabetes with insulin resistance. Certainly, either these pseudo-PHP women with type 2 diabetes have a mutation in the Gsα protein or nearby genome for its susceptibility to type 2 diabetes, or they represent just a phenomenon of coincidence. Further evaluation and collection of cases are necessary to define the possible role and interrelationship of pseudo-PHP and type 2 diabetes.

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High Prevalence of Albuminuria Among African-Americans With Short Duration of Diabetes

There is controversy regarding the prevalence of albuminuria in urban African-American patients with newly diagnosed type 2 diabetes. In Atlanta, we found significant albuminuria in 30–36% of patients with diabetes of <1 year's duration (1), while the New York sample described by Chaiken et al. (2) had a prevalence of only 3%. To resolve this issue, we examined albumin excretion in a large group of patients with type 2 diabetes.

Between October 1992 and January 1998, 3,091 African-American patients with type 2 diabetes presented to the Grady Diabetes Clinic for a first visit and had measurements of urine albumin excretion. As described previously (1), albumin-to-creatinine ratios were measured in untimed urine specimens; such determinations correlate well with measurements of 24-h urine albumin (1,2). Patients were divided into those with diabetes diagnosed either <1 year (n = 1,533) or ≥1 year previously (n = 1,558).

Patients with diabetes duration ≥1 year, compared with those with duration <1 year, had significantly higher age (53.9 years vs. 51.0 years), HbA_{1c} (9.5 vs. 9.2%), mean blood pressure (96 vs. 93 mmHg), and serum creatinine (97 vs. 88 μmol/l) ($P < 0.01$ for each comparison). Of patients with duration <1 year, 20% had microalbuminuria (30–300 mg/g creatinine) and 4% had nephropathy (>300 mg/g). Corresponding prevalences for those with duration ≥1 year were significantly higher, at 26 and 13%, respectively ($P < 0.05$). Even normotensive patients with diabetes duration <1 year had a 17% rate of microalbuminuria and a 2% rate of nephropathy. Hypertensive patients with diabetes of any duration had a significantly increased rate of microalbuminuria and nephropathy compared with normotensives ($P < 0.05$). Thus, both hypertension and longer duration of diabetes increased the prevalence of significant albuminuria.

To determine contributing factors, we performed stepwise regression. In patients with known duration of diabetes <1 year, the quantity of albuminuria correlated positively with higher levels of systolic blood pressure, serum creatinine, fasting plasma glucose, BMI, male sex, and fasting plasma C-peptide. Other parameters, such as age, diastolic blood pressure, and HbA_{1c}, did not contribute significantly. When patients with diabetes of any duration were considered, albuminuria correlated positively with systolic blood pressure, fasting C-peptide, fasting serum glucose, HbA_{1c}, serum creatinine, age, and duration of diabetes.