Impaired Absorption of Insulin Aspart From Lipohypertrophic Injection Sites

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Lipohypertrophy is a common side effect of subcutaneous insulin therapy, occurring in up to 50% of patients with type 1 diabetes (1–3). It is generally held that absorption of insulin from such palpably abnormal sites is erratic, although the consequence thereof on glucose control has been considered controversial (1,4,5). Notably, a recent study using the continuous glucose monitoring system to monitor swings of blood glucose documented a significant correlation between the mean of daily differences of glucose and the severity of injection site lipohypertrophy (6). Few studies have investigated insulin uptake from lipohypertrophic tissue. Absorption of isophane (NPH) insulin, as determined by plasma free insulin, was found to be markedly defective at abnormal injection sites (7), and absorption of regular insulin (Actrapid) was delayed as determined by the clearance of ^{125}I-insulin (8). It was concluded from these studies that the differences were of sufficient magnitude to be of clinical importance. Currently, both of these insulin preparations give way to insulin analogs. Therefore, the present study was conducted to investigate whether the absorption of a single subcutaneous dose of insulin aspart is impaired when administered to lipohypertrophic tissue in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Nine male patients (51.6 ± 5.4 years of age [means ± SE; range 22–69], HbA_{1c} 7.3 ± 0.4% [ref. <5.2%], BMI 24.3 ± 1.0 kg/m^2, and duration of diabetes 34.9 ± 5.1 years) were recruited from the Diabetes Day Care Unit at Danderyd University Hospital. Selection of subjects was based on the detection of a visible, palpable, and massive thickening of fat tissue with higher consistency and grade of lipohypertrophy at the site of injection and a diameter of 6–10 cm. No patient had measurable plasma C-peptide levels (ref. <0.1 nmol/l). Seven patients were treated with multiple daily injection therapy and two with continuous subcutaneous insulin infusion. Their mean daily insulin dose was 53.6 ± 4.2 units, which included a breakfast insulin dose of 5.8 ± 1.3 units. The local ethics committee of Karolinska Hospital approved the study protocol, and all subjects provided written informed consent.

The study was a randomized crossover trial. The patients on multiple daily injections had taken their bedtime dose of insulin before 10:00 P.M., and the pump patients had a constant basal infusion rate during the test. No hypoglycemic event (blood glucose ≤3.5 mmol/l) was reported 12 h prior to testing. Each patient performed two absorption tests in random order separated by a minimum of 7 days. Patients arrived at the clinical research center at 7:30 A.M. after an overnight fast of no less than 7 h. An indwelling catheter was inserted in an antecubital vein to obtain blood samples for free insulin and blood glucose determinations. Blood samples were taken before the insulin injection and thereafter at 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 210, 240, 270, 300, and 330 min. A diabetes nurse specialist injected 10 units NovoRapid (Novo Nordisk, Bagsværd, Denmark) subcutaneously in the abdominal wall using an 8-mm needle at 90° to the skin surface with a two-finger "pinch-up" technique. A standardized breakfast, which had an energy content of 405 kcal and a nutrient content of 22 g protein, 8 g fat, and 60 g carbohydrate, was served immediately thereafter.

Free insulin was measured after polyethylene glycol precipitation by Mercodia Iso-Insulin (ELISA; Mercodia, Uppsala, Sweden) using a two-site enzyme immunoassay containing two monoclonal antibodies (9,10). Blood glucose was analyzed with the Hemocue method (Hemocue, Ängelholm, SE). Data are presented as means ± SE. Statistical analyses were made using StatView software (version 5.0.1; SAS Institute, Cary, NC). Differences between groups were tested with Wilcoxon's signed-rank test. Areas under the curve (AUCs) were calculated with the trapezoidal method. Statistical significance was assigned for P values <0.05.

RESULTS

— The fasting plasma free insulin concentration was 26 ± 10 pmol/l before insulin injection in lipohypertrophic tissue and 24 ± 8 pmol/l before insulin injection in normal tissue (P = 0.674). A higher C_{max} of plasma insulin was observed after injection in normal tissue (226 ± 32 pmol/l) than in lipohypertrophic tissue (169 ± 33 pmol/l; P = 0.015), with significantly higher insulin levels recorded between 40 and 90 min (Fig. 1). Time to maximal insulin concentration was 43 ± 5 min after insulin injection in lipohypertrophic tissue compared with 56 ± 5 min after insulin injec-

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Abbreviations: AUC, area under the curve.

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

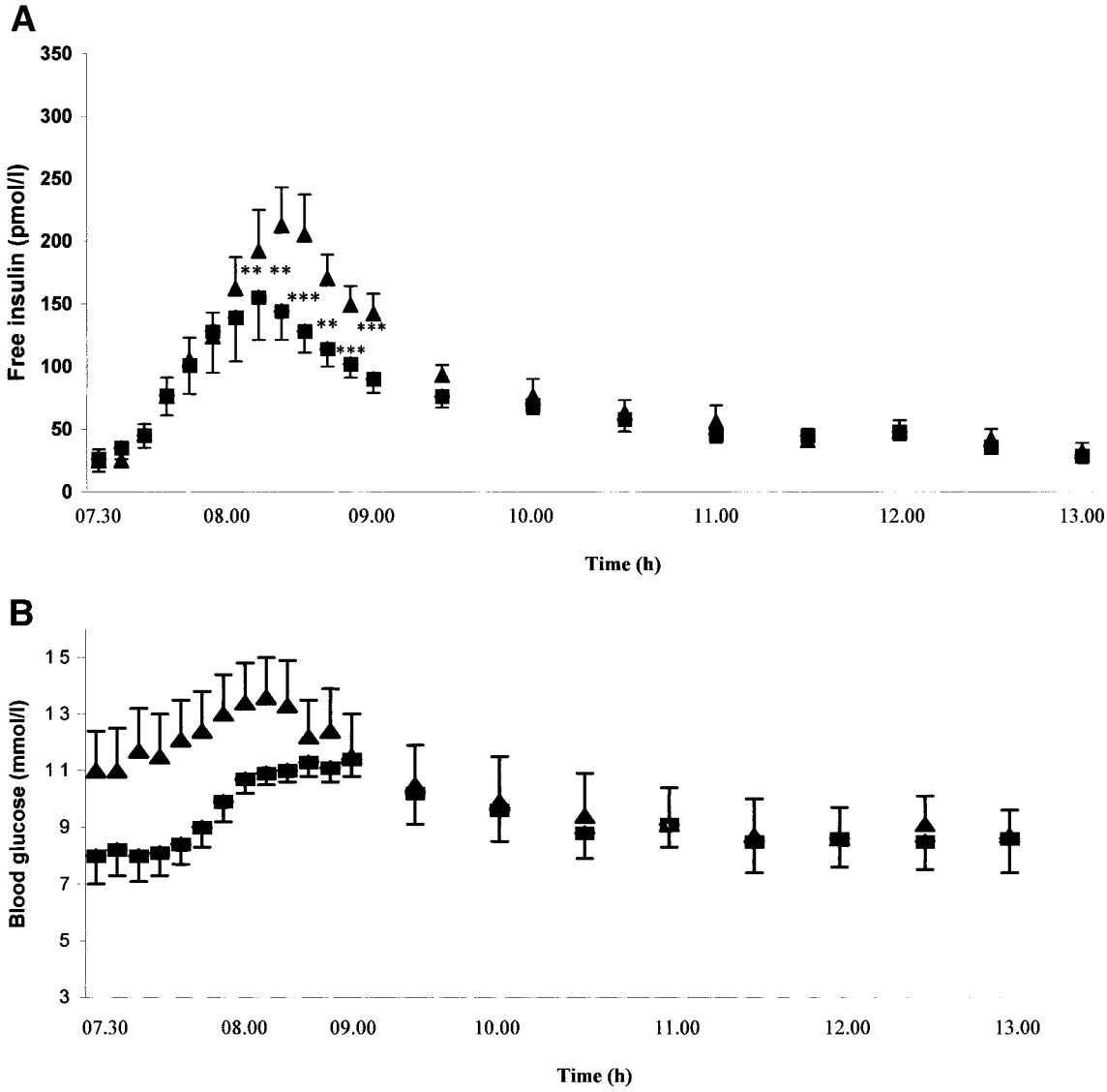

Figure 1—*Plasma concentrations of free insulin* (A) *and blood glucose* (B) *in nine type 1 diabetic patients after a 10-unit subcutaneous injection of insulin aspart in normal tissue* (▲) *versus lipohypertrophic tissue* (■) *at 7:30* A.M., *immediately before breakfast. Values are means ± SE.* *P < *0.05,* **P < *0.01,* ***P < *0.001.*

tion in normal tissue ($P = 0.102$). The $AUC_{0-240\ min}$ was 294 ± 36 (normal tissue) versus 230 ± 39 (lipohypertrophic tissue) ($P = 0.051$). Fasting blood glucose was 8.0 ± 1.0 mmol/l before injection in lipohypertrophic tissue versus 11.0 ± 1.4 mmol/l before injection in normal tissue ($P = 0.097$). Blood glucose profiles are given in Fig. 1.

CONCLUSIONS — In the present study, we found that the absorption of insulin aspart was impaired in lipohypertrophic tissue, yielding a 25% lower C_{max} of plasma insulin. We believe that this is an effect that is likely to be of clinical importance. When comparing abdominal injections of regular insulin below and above the umbilicus in nine type 1 diabetic patients, it was demonstrated that, namely, a 28% greater area under the plasma insulin curve was associated with a more pronounced plasma glucose–lowering effect (11). Due to the cross-over design of our study, systemic factors affecting insulin absorption and degradation would be expected to be similar during absorption from normal and lipohypertrophic tissue. It has been speculated upon whether local degradation of insulin takes place in lipohypertrophic tissue to such an extent as to explain differences in plasma insulin profiles obtained after a single injection (7). The shape of the plasma free insulin profiles obtained in this study with a similar initial rise of free insulin after injection in either normal or lipohypertrophic tissue but a lower C_{max} and a lower AUC in lipohypertrophic tissue is compatible with an increased local degradation of insulin aspart after injection in lipohypertrophic tissue. The question of whether local degradation of injected insulin takes place in humans remains to be further explored. Notably, using a biopsy technique, local degradation of insulin was

demonstrated in pigs in 1979 (12). The present study demonstrates that impairment of insulin absorption from lipohypertrophic sites also takes place with analog insulins. Further studies are needed to ascertain the clinical meaning of our findings, particularly in respect to the size and consistency of lipohypertrophy. It is suggested that diabetic patients should be advised to refrain from injecting insulin aspart into lipohypertrophic subcutaneous tissue.

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