Absorption of Rapid-Acting Insulin in Obese and Nonobese NIDDM Patients

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OBJECTIVE — To study the absorption rate of rapid-acting insulin from subcutaneous injection sites in nonobese and obese non-insulin-dependent diabetes mellitus (NIDDM) patients.

RESEARCH DESIGN AND METHODS — Ten nonobese and 10 obese NIDDM patients (body mass indexes 24.1 ± 0.4 and 31.4 ± 0.8 kg/m^2, respectively) received four subcutaneous injections of ^{125}I-labeled rapid-acting insulin (Actrapid Human, 5 U): three in the abdominal wall above, lateral to, and below the umbilicus; and one in the thigh. The depth of the subcutaneous fat layer was measured using ultrasound techniques. The residual radioactivity was monitored externally for 270 min.

RESULTS — The disappearance half-life of ^{125}I-insulin was between 4 and 6 h from all injection sites, with the exception of the upper abdominal area in the nonobese subjects, where it measured ~3 h. The residual radioactivity did not differ between nonobese and obese patients measured from any of the sites. In the nonobese group, the most rapid absorption of ^{125}I-insulin was found from the upper abdominal area and the slowest from the thigh. In the obese group, the absorption rates did not differ between sites. No correlation was found between the depth of the fat layer and the residual radioactivity when measured at any site.

CONCLUSIONS — Our results indicate that the absorption of rapid-acting insulin is markedly slow in both obese and nonobese NIDDM patients compared with IDDM patients and healthy subjects studied previously. In the nonobese group, the most rapid absorption of ^{125}I-insulin is obtained after injection into the upper abdominal area. Inter- and intraregional differences are small in the obese patients. Consequently the choice of injection site is of little importance in this group.

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BMI, body mass index; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; SU, sulfonylurea.

Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by increased insulin resistance and/or decreased insulin secretion (1,2). Treatment for NIDDM is usually initiated with diet alone and if this is not sufficient, sulfonylurea (SU) is added. According to World Health Organization criteria (3), metabolic control is unsatisfactory in 10–50% of patients treated with diet and SU after 10 years of diabetes duration (4–7). In a recent study (8), the number of patients treated with insulin as a result of secondary SU treatment failure has been estimated to be ~40% after 10 years duration and 60% after 15 years duration. Recent studies of insulin-dependent diabetes mellitus (IDDM) patients have demonstrated that intensified insulin treatment, compared with standard treatment, retards the development of microvascular complications (9,10). Although there are no comparable studies in NIDDM patients, many patients in whom SU treatment failed are treated with insulin in attempts to reduce the risks for micro- and macrovascular complications.

Insulin absorption is a factor of major importance for glucose control in insulin-treated diabetic patients (11,12). To date insulin absorption has mainly been studied in IDDM patients and in healthy subjects (11–14). Thus, the aim of this study was to determine the absorption rate of rapid-acting insulin in NIDDM patients after injection into various subcutaneous areas and to evaluate the importance of the injection site in insulin treatment of obese and nonobese patients with NIDDM.

RESEARCH DESIGN AND METHODS

— Twenty patients with NIDDM were included in the study and divided into two groups according to body mass index (BMI) (weight/height^2). Study inclusion criteria for the participants included the following: age at onset >35 years, fasting C-peptide level ≥0.3 nmol/l, and successful diet and/or SU treatment >1 year after diagnosis. Exclu-

Table 1—*Characteristics of the NIDDM patients*

	n	Sex (M/F)	Age (years)	BMI (kg/m^2)	Known diabetes duration (years)	HbA_{1c} (%) (3.5–5.5)	Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)
Nonobese	10	8/2	58 ± 2	24.1 ± 0.4	9 ± 2	7.7 ± 0.4	0.50 ± 0.11
Obese	10	5/5	59 ± 2	31.4 ± 0.8*	10 ± 2	9.4 ± 0.6†	0.57 ± 0.09

Data are means ± SE. Normal range for HbA_{1c} is 3.5–5.5%. *$P < 0.001$; †$P < 0.05$ obese vs. nonobese NIDDM patients.

sion criteria for the study included a positive diagnosis for thyroid disease and/or severe diabetic neuropathy. Clinical characteristics of the study participants are presented in Table 1. The obese and nonobese group differed only with regard to BMI, HbA_{1c}, and the male/female ratio. The latter might have some influence on the results, but there are no studies showing differences in insulin absorption between men and women, nor in healthy subjects or IDDM patients. One patient in the nonobese group had simplex retinopathy, and one obese participant had nephropathy (albuminuria).

Four patients were treated with β-blockers (three obese patients treated with atenolol, 25, 75, and 100 mg, respectively, and one nonobese patient treated with metoprolol, 200 mg) and four with calcium antagonistic agents (two obese patients treated with verapamil, 240 mg, and felodin, 10 mg, respectively, and two nonobese patients treated with verapamil, 240 mg, and diltiazem, 180 mg, respectively).

The patients arrived at the hospital after an overnight fast. One hour before the experiment, the patients received 100 mg potassium iodide orally to block thyroid uptake of radioactive iodide. On the 3 consecutive days the participants received 50 mg of iodide.

The depth of the fat layer at the four injection sites was measured using two-dimensional ultrasound with a linear scanner (7 MHz, Acuson, Mountain View, CA). Thereafter the patients were served a standardized breakfast (1,810 kJ, 433 kcal) consisting of 1 cup (150 ml) decaffeinated coffee or tea, 100 ml orange juice, 200 ml sour milk with 100 ml cereal, two slices of bread with 10 g margarine, 15 g cheese, and 10 g ham. Immediately after breakfast, radiolabeled rapid-acting insulin (^{125}I-Actrapid, 5 U, 10 kBq, 0.05 ml, 100 U/ml; Novo, Copenhagen, Denmark) was injected subcutaneously into four injection sites. The four injections were done in the same order in all patients; each injection finished within 5 s. The total time from the start of the first injection to the end of the last injection was ~2 min in each patient. The injection sites were located as follows: *1*) 120 mm above, 2) 120 mm lateral to, and 3) 40 mm below the umbilicus, and 4) in the thigh (midline), one-third of the distance between the inguinal ligament and upper part of the patellae. The injections were made at a standard speed and were based on a previous ultrasound determination. The injections were administered into the middle of the fat layer. The patients remained in a supine position during the test except between 180 and 210 min, when a standardized lunch was served. At this time the patients maintained a sitting position. The room temperature was kept between 22 and 24°C.

The residual radioactivities were measured continuously every minute by means of four collimated detector systems (50 mm diameter × 25 mm height; Leab, Molnlycke, Sweden) mounted ~100 mm above the skin surfaces. The collimated detectors were interfaced to a multichannel spectrometer (ND 600, Nuclear Data, Schaumburg, IL). After the experiment, the data were transferred to a microcomputer (Apple II, Apple, Cupertino, CA) for subsequent analysis.

The residual radioactivity at the injection site, expressed as percentage of initial, was calculated every 30 min as the mean of ten 60-s intervals, e.g., the 120-min value was calculated as the mean value of the counts between 116 and 125 min. All values are expressed as means ± SE. Levels of significance were tested using two-tailed Student's *t* test. When multiple comparisons were performed, one-way analysis of variance with Fisher's test was used. To assess ratios, the Kruskal-Wallis test was applied. Correlation coefficients were calculated using a standard procedure. A *P* value < 0.05 was considered statistically significant.

RESULTS

Plasma glucose

The basal plasma glucose values before breakfast, 9.2 ± 0.7 and 10.3 ± 0.7 mmol/l (NS), and before insulin injections, 11.2 ± 0.9 and 12.6 ± 1.3 mmol/l (NS), were similar in the obese and nonobese subjects. As expected, there was a tendency for lower plasma glucose values in the nonobese group during the course of the experiment, but these differences were not statistically significant at any individual point (Fig. 1). The reduction in plasma glucose between 0 and 180 min was significantly greater in the nonobese group compared with that of the obese subjects ($P < 0.05$). One of the nonobese patients was given glucose orally after 180 min because of a plasma value of 2.9 mmol/l.

Depth of the fat layer

The depth of the fat layer at the injection sites was significantly greater in obese than nonobese patients measured above, below, and lateral to the umbilicus. How-

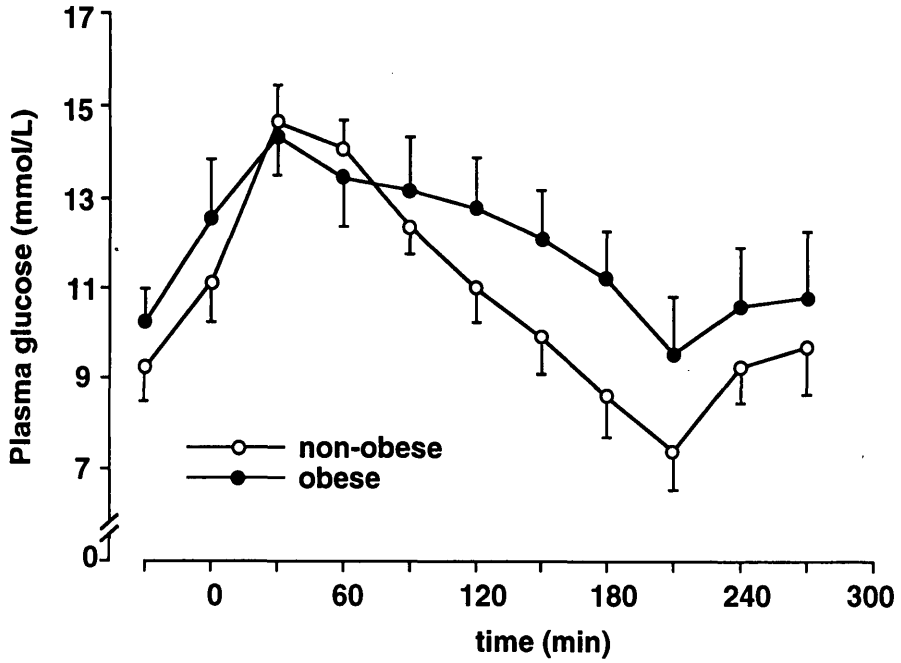

Figure 1—*Plasma glucose concentration in 10 obese and 10 nonobese NIDDM patients after injection of 5 U ^{125}I-labeled rapid-acting insulin in four subcutaneous sites. Values are means ± SE.*

ever, in the thigh the difference in fat depth between the groups did not reach statistical significance ($P = 0.06$, NS) (Table 2). Within the nonobese patient group, the thigh showed a significantly thinner fat layer than the site measured above as well as below the umbilicus.

Residual ^{125}I radioactivity

The half-life of the disappearance of ^{125}I-insulin in both obese and nonobese patient groups ranged between 4 and 6 h from all injection sites, except the upper abdominal area measured in the nonobese subjects. When measured at this site the half-life of the disappearance of ^{125}I-insulin was ~3 h (Table 3 and Figs. 2 and 3). The residual radioactivities 4.5 h after injection, in the obese group were 39, 55, 47, and 53% for the upper, lower, the lateral areas of the abdomen and the thigh, respectively, whereas in the nonobese group, the respective residual radioactivities were 29, 48, 43, and 60% (intergroup differences NS).

Although the depth of the fat layers differed significantly between the obese and nonobese patients, there were no significant intergroup differences in residual radioactivity between any of the injection sites (Table 3 and above).

The absorption rates from the various injection sites within the nonobese group differed significantly, the highest rates being found from the upper abdominal area and the lowest rates from the thigh (Fig. 2). However, in the obese group, the differences between the injection sites were small and statistically insignificant (Fig. 3).

From the log-activity versus time plot, it is apparent that the absorption rate increases continuously over time, and this response is most prominent in the upper abdominal area in the nonobese group.

When studied separately, there were no differences between patients treated with β-blockers or calcium antagonistic agents versus untreated patients with respect to residual activity measured at any of the four sites.

Correlations

Depth of the fat layer was not significantly correlated with the residual radioactivity measured at any of the injection sites of either group. Furthermore, when all abdominal injections were analyzed together, depth of the fat layer was not correlated with residual radioactivity.

CONCLUSIONS— The present study offers the first detailed report of the absorption kinetics of insulin in patients with NIDDM. We here demonstrate that the absorption of rapid-acting insulin is considerably slower in this patient group, NIDDM patients, regardless of obesity, when compared with previously studied IDDM patients (12,14). The absorption rates of a similar dose of rapid-acting insulin from subcutaneous injection sites in the abdominal wall and in the thigh were between 15 and 45% lower in our NIDDM patients compared with IDDM patients studied previously under identical conditions (14).

Table 2—*Depth of the fat layers at the injection sites*

Region	Fat layer depth (mm)	
	Nonobese	Obese
Abdomen		
Above umbilicus	14.2 ± 1.0‡	22.3 ± 2.8*
Lateral to umbilicus	12.1 ± 1.0	20.1 ± 2.4†
Below umbilicus	13.8 ± 1.1	21.9 ± 2.8†
Thigh	9.7 ± 1.4	14.9 ± 2.3

Data are means ± SE. *$P < 0.05$; †$P < 0.01$ obese vs. nonobese. ‡$P < 0.01$ above umbilicus vs. thigh, nonobese.

Table 3—*Time to 50% elimination ($t_{1/2}$) of rapid-acting insulin (5 U) after subcutaneous injection in abdomen and thigh in 10 nonobese and 10 obese NIDDM patients*

Region	$t_{1/2}$ (min)	
	Nonobese	Obese
Abdomen		
Above umbilicus	196 ± 13*†	242 ± 22
Lateral to umbilicus	250 ± 22†‡	274 ± 25
Below umbilicus	290 ± 22	297 ± 24
Thigh	355 ± 24	304 ± 28

Data are means ± SE. *$P < 0.001$ vs. thigh, nonobese. †$P < 0.05$ vs. below umbilicus, nonobese. ‡$P < 0.01$ vs. thigh, nonobese.

Low insulin absorption rates were observed not only in the obese NIDDM patients, but also in the NIDDM patients with normal body weight. This finding is contrary to previous findings in IDDM patients, whereby an inverse relationship between the insulin absorption rate and the degree of adiposity measured in various ways has been observed (14–16). The insulin absorption rate did not correlate with the depth of the fat layer in our NIDDM patients. In fact, the lowest absorption rate was measured in the thigh in the nonobese subjects, a region that showed the thinnest fat layer. This finding suggests that the regulation of insulin absorption is different in NIDDM patients compared with that of IDDM patients.

Subcutaneously injected rapid-acting insulin displays a characteristic course of absorption in healthy subjects and IDDM patients, with an absorption rate increasing continuously over time (12,17). This pattern of absorption has convincingly been demonstrated to be caused by the successive dissociation of insulin hexamers into smaller units, dimers and monomers, a phenomenon that seems to interact with blood flow (17). The same pattern of absorption, although less pronounced, was also observed in our NIDDM patients and most clearly in sites with relatively rapid absorption, i.e., from the upper abdominal area in nonobese patients. One possible mechanism for the low absorption rate of rapid-acting insulin in NIDDM patients might be a retarded rate of dissociation of the hexameric insulin. Whether a low blood flow might be a common denominator behind such a response is not known.

Some of our patients were treated with drugs having vasoactive properties. Four patients received β-blocking agents, and four other patients received calcium antagonistic agents. Unselective β-blockade, which has previously been demonstrated to reduce peripheral blood flow, may retard insulin absorption, whereas calcium antagonistic agents, acting vasodilatory, have the opposite effect (18). In the previous study, high doses of the blocking agents were given, whereas our patients received much smaller doses. The insulin absorption rates in our study did not differ between the treated and the untreated patients.

Regardless of the mechanism behind the low insulin absorption rate in the NIDDM patients, increased age may play a contributory role. One study suggests that older individuals absorb insulin more slowly than young subjects (19). However, the differences reported by those investigators were not statistically significant, and in another investigation, no influence of age on the absorption of isophane insulin could be observed (20).

In addition to age, the diabetic state as such might influence the insulin absorption rate. The plasma glucose level has been suggested as a factor of importance to insulin absorption. Thus, hypoglycemia has been found to depress the absorption rate, whereas ketoacidosis seems to have the opposite effect (19,21). In our study plasma glucose varied between 8 and 14 mmol/l and is therefore unlikely to be coupled with the low insulin absorption rate in our NIDDM patients. The explanation for the slow insu-

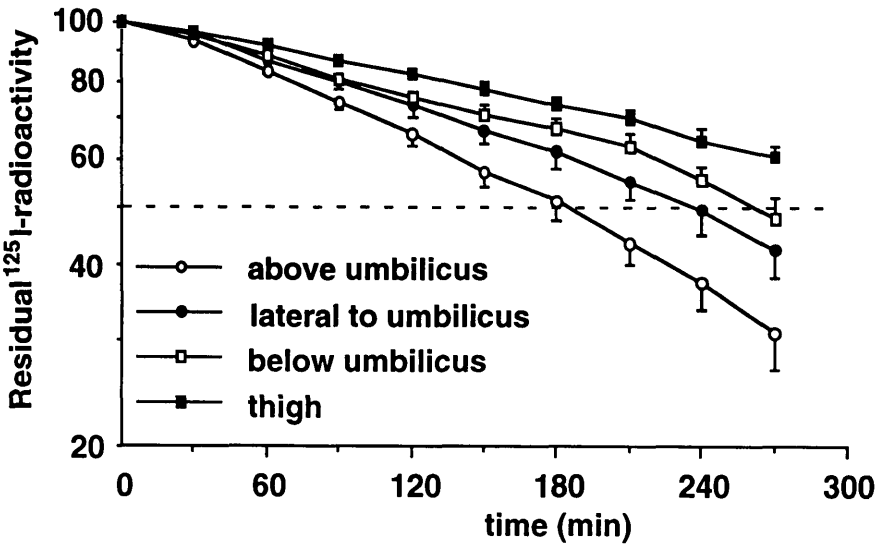

Figure 2—*Residual ^{125}I-radioactivity measured at four subcutaneous injection sites in 10 nonobese NIDDM patients after the injection of 5 U ^{125}I-labeled rapid-acting insulin. Values are means ± SE.*

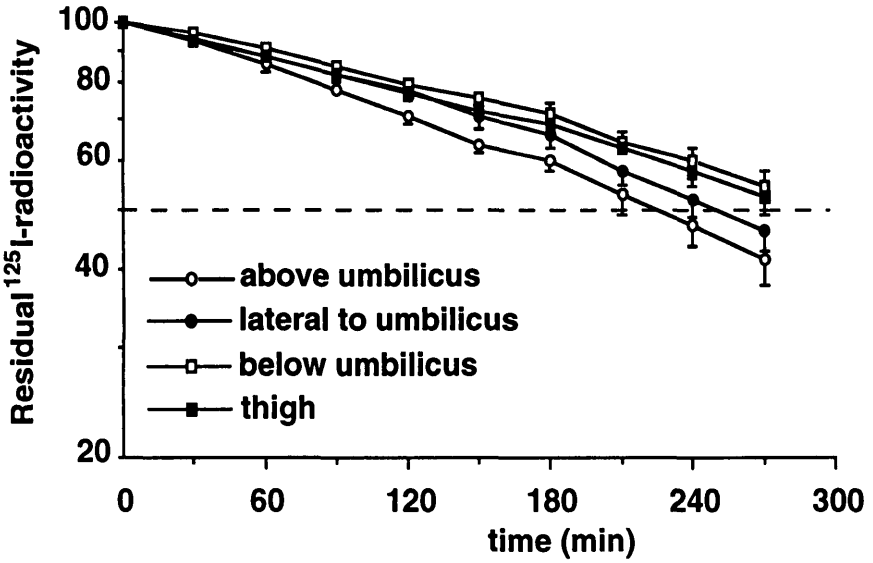

Figure 3—*Residual ^{125}I radioactivity measured at four subcutaneous injection sites in 10 obese NIDDM patients after the injection of 5 U ^{125}I-labeled rapid-acting insulin. Values are means ± SE.*

lin absorption in NIDDM is unclear and deserves further elucidation.

The slow insulin absorption in the NIDDM patients may perhaps partly explain the only minor differences in glycemic control between NIDDM patients on varying insulin regimens. In a recent study of four different treatment strategies in NIDDM patients receiving maximal dose of sulfonylureas, regardless of whether treatment was given with sulfonylurea and evening NPH insulin, sulfonylurea and morning-NPH insulin, two insulin injections a day (mixture of rapid-acting and NPH insulin), or multiple injections (rapid-acting insulin before meals and evening NPH insulin), no difference in HbA_{1c} could be demonstrated (22). The low insulin absorption rates in the NIDDM patients may perhaps also contribute to the hyperinsulinemia that was found in the two groups treated with either two or four injections per day. With a half-life of the rapid-acting insulin approaching 6 h, clearly insulin will be eliminated in parallel from several depots, and this will contribute to a steady, high level of the peptide in plasma.

When the diabetic patient is treated with rapid-acting insulin, it is important to know which parts of the subcutaneous area offer the most rapid rate of insulin absorption. In IDDM patients, the highest absorption rates of insulin occur in the epigastric area (14). This finding for IDDM patients applies also to our NIDDM patients with normal body weight. However, in the obese group, differences between the various injection sites were minimal. Therefore, changing the injection site in obese NIDDM patients cannot be used as a strategy to enhance the absorption of insulin as recommended for IDDM patients.

Since retardation of the rate of dissociation of the hexameric insulin may be an important factor in the delayed insulin absorption in NIDDM patients, treatment strategies promoting this dissociation process should be tested. Sprinkler needle injection or massage of injection sites, which enhance the absorption of rapid-acting insulin (23,24), probably mainly by accelerating hexamer dissociation (17), might be especially suitable in this patient category.

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