Diabetic Lipohypertrophy Delays Insulin Absorption

ROBERT J. YOUNG, M.R.C.P., W. JAMES HANNAN, Ph.D., BRIAN M. FRIER, M.D., JUDITH M. STEEL, F.R.C.P., AND LESLIE J. P. DUNCAN, F.R.C.P.

The effect of lipohypertrophy at injection sites on insulin absorption has been studied in 12 insulin-dependent diabetic patients. The clearance of ^{125}I-insulin from sites with lipohypertrophy was significantly slower than from complementary nonhypertrophied sites (% clearance in 3 h, 43.8 ± 3.5 ± SEM) control; 35.3 ± 3.9 lipohypertrophy, $P < 0.05$). The degree of the effect was variable but sufficient in several patients to be of clinical importance. Injection-site lipohypertrophy is another factor that modifies the absorption of subcutaneously injected insulin. DIABETES CARE 1984; 7:479–80.

Although diabetic lipoatrophy has been virtually eradicated by the use of highly purified porcine insulins, lipohypertrophy at insulin injection sites is now found frequently.[1] Since lipohypertrophy is due largely to the local pharmacologic (lipogenic) effects of insulin,[2] this is not surprising and, indeed, lipohypertrophy has recently been reported in patients receiving only human insulin.[3]

Lipohypertrophy will therefore continue to be a side effect of subcutaneous insulin administration. In clinical practice we have noticed that the insulin requirements of patients sometimes fall abruptly when they are advised to avoid their lipohypertrophied injection sites. But lipohypertrophy is not a recognized cause of variation in insulin absorption.[4–6] We have investigated the effect of lipohypertrophy at the injection site on insulin absorption in 12 diabetic individuals by comparing the clearance of ^{125}I-insulin injected simultaneously into two anatomically mirror image sites with and without lipohypertrophy.

PATIENTS AND METHODS

Twelve insulin-dependent diabetic patients with easily visible as well as palpable lipohypertrophy at their regular injection site were studied. All had given informed consent to the study, which had been approved by the local physicians' advisory ethical committee. They were using twice-daily highly purified porcine insulins. Pretreatment was carried out with potassium iodide to prevent accumulation of radioiodine in the thyroid. The usual morning dose of short-acting insulin was given as two equal portions of Actrapid-MC (Novo Company Limited, Basingstoke, United Kingdom), each containing approximately 0.1 μCi ^{125}I-insulin (Actrapid-MC, 40 strength labeled with ^{125}I at tyrosine A14 and supplied by Novo Company Limited). The disappearance of ^{125}I-labeled insulin from injection sites has been shown previously to correlate precisely with the appearance of insulin in plasma.[7,8] In studies 1–8 each portion of Actrapid was mixed with half the usual morning dose of intermediate insulin in the form of Monotard-MC 40 strength. One portion was injected into the center of a lipohypertrophy pad and, at the same time, the other portion was injected into the most closely complementary anatomic site without lipohypertrophy on the opposite side of the body. All injections were made with $\frac{3}{8}$" 27G needles inserted perpendicular to the skin surface up to the hilt. The rate of insulin absorption was determined by monitoring the clearance of ^{125}I from the injection site using a sodium-iodide crystal and photomultiplier assembly coupled to a portable nucleonics system (Model MS310, Alrad Instruments Ltd., Newbury, United Kingdom). The 2"-diameter by 0.5"-thick sodium-iodide detector was housed in a cylindric lead shield with a thin clear perspex front cover. This reduced the background counts while allowing the detector to be repositioned accurately over the injection site. Duplicate measurements of at least 5000 counts were made at 10-min intervals up to 3 h. The detected count rate was then plotted as a function of the time after injection and the best fit to the data obtained.

RESULTS

Details of the subjects and clearance of ^{125}I-insulin from the two injection sites are shown in Table 1. Analysis of the differences in absorption rates between the two sites by either

TABLE 1
Clearance of subcutaneously injected ^{125}I-insulin from lipohypertrophy pads and complementary control sites in 12 insulin-dependent diabetic patients

Subject				% ^{125}I-insulin cleared in 3 h	
No.	Sex	Age	Site	Control	Lipohypertrophy
1	F	27	Arm	26.7	34.9
2	M	19	Abdomen	63.0	64.7
3	M	17	Leg	55.1	25.7
4	F	18	Arm	44.5	32.7
5	M	24	Abdomen	37.3	26.3
6	M	33	Leg	44.3	27.5
7	M	28	Leg	34.7	39.5
8	F	23	Leg	34.7	32.3
9	F	16	Abdomen	55.0	44.0
10	M	20	Abdomen	52.0	54.0
11	F	21	Arm	26.0	17.0
12	F	21	Arm	52.0	25.0
Mean (± SEM)				43.8 ± 3.5*	35.3 ± 3.9*

*Difference between means significant ($P < 0.05$)—paired *t*-test.

a paired *t*-test or a Wilcoxon paired sample test confirmed that the mean clearance from the lipohypertrophy site was significantly slower ($P < 0.05$) than from the control site though there was marked interindividual variation in the degree of the effect observed.

DISCUSSION

The retarding effect of lipohypertrophy on insulin absorption was of sufficient magnitude to be of clinical importance in some patients. This accords with our clinical impressions of the effect of lipohypertrophy on diabetes control. Subjectively, the delay was proportional to the extent of lipohypertrophy but this was impossible to quantify in the small areas involved. However, insulin absorption in subjects of varying general adiposity has recently been related to skinfold thickness.[7]

The rate of insulin absorption is already recognized to be influenced substantially by various factors including the anatomic site of injection, exercise, environmental temperature, and the rate of subcutaneous insulin degradation.[4,5] This study demonstrates yet another factor that may influence the management of subcutaneous insulin regimens by contributing to the increasingly recognized variation in insulin absorption kinetics. The current prevalence of lipohypertrophy[7] means that its functional as well as cosmetic importance should probably be considered more frequently.

ACKNOWLEDGMENT: We are most grateful to Novo Company Limited for supplying the ^{125}I-insulin preparation.

From the Diabetic Department and Department of Medical Physics, Royal Infirmary, Edinburgh, Scotland.

Address reprint requests to R. J. Young, M.R.C.P., Diabetic Department, Royal Infirmary, Edinburgh, Scotland EH3 9YW.

REFERENCES

[1] Young, R. J., Steel, J. M., Frier, B. M., and Duncan, L. J. P.: Insulin injection sites in diabetes—a neglected area? Br. Med. J. 1981; 283:349.

[2] Renold, A. E., Marble, F., and Fawcett, D. W.: Action of insulin on deposition of glycogen and storage fat in subcutaneous tissue. Endocrinology 1950; 46:55–66.

[3] Galloway, J. A., Peck, F. B., Fineberg, S. E., et al.: The U.S. "New Patient" and "Transfer" studies. Diabetes Care 1982; 5 (Suppl. 2):135–39.

[4] Editorial: Subcutaneous injections and absorption of insulin. Lancet 1980; 1:1005–1006.

[5] Koivisto, V. A.: Sauna-induced acceleration in insulin absorption from subcutaneous injection site. Br. Med. J. 1980; 282:1411–13.

[6] Paley, R. G., and Scott, M. H.: Severe insulin lipodystrophy as a possible cause of instability in diabetics. Br. Med. J. 1958; 2:1331–34.

[7] Britwell, A. J., Owens, D. R., Luzio, S., Jones, I. R., Hayes, T. M., and Volund, A.: Subcutaneous adiposity influences absorption of radiolabelled actrapid insulin. Diabetologia 1983; 25:141.

[8] Strom, H., Lorentzen-Lund, S., Dahl-Jorgensen, K., Torjesen, P., and Hansen, K.: Insulin absorption kinetics: comparison of disappearance of iodinated insulin and appearance of "free" insulin in blood. Diabetologia 1983; 25:196.