Insulin Absorption from the Abdomen and the Thigh in Healthy Subjects During Rest and Exercise: Blood Glucose, Plasma Insulin, Growth Hormone, Adrenaline and Noradrenaline Levels

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Summary. Insulin was absorbed faster from the abdomen than from the thigh under resting conditions and during exercise. Exercise enhanced the rate of insulin absorption marginally. The fall of blood glucose during rest and exercise was not significantly different after insulin injection into either site. The faster absorption of insulin from the abdomen during rest and exercise was reflected in a sharper rise of serum growth hormone levels and urinary adrenaline excretion. Therefore exercise should not be taken immediately after injection of a large dose of soluble insulin, particularly into the abdomen.

Key words: Insulin, insulin absorption, plasma insulin, blood glucose, exercise, growth hormone, urinary catecholamines.

Physical exercise is one of the three corner stones of the treatment of the insulin-dependent diabetic. However, the fluctuations of blood glucose during exercise often exceed the desirable range. Previous investigations have shown that the rate of absorption of subcutaneously injected insulin varies during physical exercise depending on the site of injection [1–4] in man and rat. These findings might explain the large variations of blood glucose during exercise, being mediated by faster absorption of insulin and/or an increased glucose uptake by the working muscle. A relatively good correlation has been established between the rate of insulin absorption and the decline of blood glucose in diabetic subjects [5–9], although it is weaker in normal subjects [9].

The aims of this study were to determine in normal subjects 1) the effect on blood glucose after injecting insulin into the thigh compared with the abdomen, 2) the concentrations of insulin in plasma and of some counter-regulatory hormones under these con-

ditions and 3) the influence of physical exercise on these metabolic indices.

Subjects and Methods

Four young healthy subjects (mean age 24.5 years, range: 21–31 years; mean weight 66.7 ± 7.1 kg and mean height 174.9 ± 7.7 cm) gave their informed consent to the following study. Each of the subjects was tested on six occasions: NaCl was injected into the arm for basal values. Actrapid insulin (Novo) was injected (0.12 U/kg body weight) 20 cm above the upper edge of the patella in the median line or 4 cm to the side of the umbilicus. The skin was folded and the depth of injection was 0.5–0.7 cm. Each test was carried out twice; once under resting conditions and a second time during exercise, consisting of 50% of the working capacity calculated according to the Pulse-Watt-Capacity 170 in the upright position (87.5 ± 6 W; ergometrical working capacity at a pulse rate of 170/min). The subjects worked three 15-min periods each separated by 5 min of rest. Venous blood samples were drawn through an indwelling catheter in the antecubital vein of the contralateral arm to the injection site at 0, 15, 45, 65, 85, 120 and 150 min. The following determinations were carried out: blood glucose (glucose oxidase, YSI-Glucose Analyser 23A), plasma insulin by radioimmunoassay (detection limit: 2.0 mU/l, inter-assay variation: 5.9%; intra-assay variation 2.2%; Behring Werke, Mahrburg, FGR), serum growth hormone by radioimmunoassay (detection limit: 1 ng/ml, inter-assay variation 6.0%; intra-assay variation: 1.8%; Behring-Werke) and urinary catecholamines according to the methods of Crout [10] and Bertler et al. [11].

Insulin absorption rates from the thigh and the abdomen were calculated from the plateau of the plasma insulin concentrations, an estimated half-life of 9.8 min [12] and a distribution volume of 20% of body weight. The sequence of the six tests in each subject was randomized. The subjects did not take any drugs for 48 h or drink alcohol or smoke for 24 h before the experiments. They were advised to sleep for at least 8 h before each experiment which started at 07.00 h. Statistical significance was calculated using the paired Student's *t* test.

Results

Figure 1 shows the blood glucose results. It did not fall after saline injection. Hypoglycaemia after insulin injection into the abdomen and the thigh did not dif-

Fig. 1. Blood glucose during rest (left) and exercise (right) after the injection of sodium chloride into the arm or insulin into the abdomen and thigh, respectively. The dose of regular insulin (Actrapid) was 0.12 U/kg body weight. Each point is the mean of the blood glucose of four normal subjects. Bars indicate SEM, the arrow the time of injection. □ = arm (sodium chloride); △ = thigh; ○ = abdomen; ▨ = period of exercise

Fig. 2. Plasma insulin levels during rest (left) and exercise (right) after the injection of sodium chloride into the arm or insulin into the abdomen and thigh, respectively. * Denotes a significant difference between insulin values after injection into the abdomen and thigh, respectively ($p < 0.001$). Symbols as in Figure 1

Fig. 3. Serum human growth hormone levels during rest and exercise after the injection of sodium chloride or insulin into the abdomen or thigh, respectively. * Denotes significant differences between the serum human growth hormone values after insulin injection into the abdomen and the thigh, respectively ($p < 0.01$). Symbols as in Figure 1

fer significantly under resting conditions and during physical exercise, but the tendency towards lower blood glucose values after injection into the abdomen was clear-cut in both conditions.

Figure 2 shows the plasma insulin concentrations. They decreased during exercise after injection of sa-

line. During rest and exercise the plasma insulin levels rose faster after insulin injection into the abdomen than into the thigh. The highest insulin level of 27.6 mU/l was reached after 45 min, i.e. after the first 15 min of exercising and it remained at this level until the 85th min. At 45 min, the difference between the in-

Table 1. Urinary adrenaline and noradrenaline excretion during rest and exercise after the injection of sodium chloride into the arm or insulin into the thigh or abdomen in four normal subjects

	Urinary noradrenaline (ng/mg creatinine)		Urinary adrenaline (ng/mg creatinine)	
	Resting	Exercise	Resting	Exercise
Arm	19 ± 1	22 ± 5	1.5 ± 0.6	2.5 ± 0.2
Thigh	20 ± 5	28 ± 6	13.6 ± 3.2	16.0 ± 5.2
Abdomen	19 ± 3	34 ± 7	19.5 ± 5.2	29.0 ± 8.5

Results given as mean ± SEM. The urine was collected from the start of the experiment (time 0) to the end (150 min)

sulin concentrations during exercise (abdomen versus thigh) was significant ($p < 0.001$; Fig. 2). The areas under the curve from 0–65 min gave a significantly higher value at rest ($p < 0.05$) and during exercise ($p < 0.001$) for the abdomen than for the thigh. The rate of insulin absorption was 0.039 and 0.027 U/min respectively for the abdomen and the thigh during exercise ($p < 0.01$).

The serum growth hormone results are presented in Figure 3. Exercise alone led to a significant increase of the growth hormone concentration ($p < 0.01$) as did insulin hypoglycaemia. During hypoglycaemia and simultaneous exercise, the highest growth hormone levels were reached. The growth hormone levels tended to increase in a steeper manner after insulin injection into the abdomen than into the thigh (NS).

Table 1 shows that noradrenaline concentrations in the urine were the same under resting conditions with and without insulin. In contrast, there was a clear-cut increase of adrenaline excretion after insulin injection during rest. Adrenaline excretion after insulin injection into the abdomen exceeded that of the thigh during rest and exercise but the differences were statistically not significant.

Discussion

The influence of physical exercise on the absorption rate of subcutaneously injected insulin is still debated [1–6, 13, 14]. ^{131}I -labelled insulin has been utilized mostly and in many studies the radioactivity above the site of injection has been measured as an index of insulin absorption [1, 2]. Kemmer et al. [15], Zinman et al. [5] and Berger et al. [3] measured the actual insulin concentration in plasma after subcutaneous injection of insulin during rest and exercise. This procedure is feasible for diabetic patients lacking insulin antibodies and normal subjects assuming a suppressed endogenous insulin release during hypoglycaemia [16].

Our results concerning insulin absorption contradict those which have been obtained with ^{131}I or ^{125}I

labelled insulin and agree with those of Kemmer et al. [15]. According to these former studies, subcutaneously injected labelled insulin is absorbed faster from the subcutaneous tissue overlying an exercising muscle than from a remote site [1–5, 13]. These former results contrast also with the general physiological principle according to which subcutaneous blood flow is shifted from the subcutaneous tissue of the exercising limbs to the trunk for reasons of thermoregulation and blood supply to the exercising muscle [9, 17–29].

The use of ^{131}I -labelled insulin is questionable for technical and methodological reasons. ^{125}I or ^{131}I rather than labelled insulin are measured over the site of injection. ^{131}I -labelled insulin degrades spontaneously in a temperature-dependent manner. Dehalogenase-activity, an enzyme abundant in subcutaneous adipose tissue, is activated by the temperature rise during exercise [30, 31] and proteases may break down insulin faster [32]. Therefore, the disappearance of radioactivity over the site of injection may not be a true estimation of insulin absorption.

According to our results, the rate of insulin absorption during exercise was significantly faster from the abdomen (0.039 ± 0.01 U/min) than from the thigh (0.027 ± 0.003 U/min; $p < 0.01$). This was confirmed by the calculation of the areas under the insulin curves between 0–65 min. The faster insulin absorption from the abdomen was reflected in lower blood glucose values, higher concentrations of serum growth hormone and increased urinary excretion of adrenaline. These results obtained with a soluble insulin preparation in normal subjects can probably be extrapolated to the use of depot insulin preparations in diabetic subjects. It can be argued that the site of injection should not be changed too often and that before exercise the thigh is preferable to the abdomen since the risk of hypoglycaemia may thus be reduced.

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