Exercise in Type 1 (insulin-dependent) diabetic patients treated with continuous subcutaneous insulin infusion

Prevention of exercise induced hypoglycaemia

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Summary. The study was performed to investigate the effects of mild to moderate exercise on blood glucose levels, metabolite concentrations and responses of counterregulatory hormones in tightly controlled Type 1 (insulin-dependent) diabetic patients treated by continuous subcutaneous insulin infusion, and to quantify the measures necessary to prevent acute and late exercise-induced hypoglycaemia. Seven male patients started a 60 min exercise period 90 min after an insulin bolus and a standard breakfast; they were monitored during a post-exercise resting period of 5 h 30 min. Different basal and premeal insulin infusion rates were applied. (Near)normoglycaemia prevailed throughout the study during the control protocol when the subjects did not exercise and received their usual insulin dose. When they exercised without changing the insulin dose, four patients were forced to stop due to hypoglycaemia. This effect of exercise could be attenuated but not completely avoided if the basal infusion rate of insulin was discontinued during the exercise period. The pronounced increase in catechol-

amine and growth hormone concentrations during exercise were not sufficient to prevent hypoglycaemic reactions. Hypoglycaemia during exercise could only be prevented when the premeal insulin bolus was reduced by 50% in addition to the discontinuation of the basal insulin infusion during exercise. In order to reduce late hypoglycaemic reactions after exercise the best measure proved to be a reduction of the basal insulin infusion rate by 25% during post-exercise hours. Administration of only 50% of the basal insulin infusion rate during this time was associated with blood glucose levels being raised up to 8 mmol/l. In conclusion, Type 1 diabetic patients treated with continuous subcutaneous insulin infusion at (near)normoglycaemia need to reduce their insulin dosage before, during, and after mild to moderate endurance exercise in order to minimize the risk of acute and late hypoglycaemia.

Key words: Exercise, Type 1 (insulin-dependent) diabetes, CSII, hypoglycaemia.

Healthy subjects usually do not have to fear any metabolic complications during physical activity. Diabetic patients, however, are faced with the risk of exercise induced hypoglycaemia or under certain conditions severe ketoacidosis [1]. Hypoglycaemia develops during physical activity because the physiological glucoregulation, i.e. an increase in hepatic glucose production precisely matching the enhanced fuel demands of the working muscle, is impaired in Type 1 (insulin-dependent) diabetic patients [2, 3]. The main reason for this defect in glucoregulation during exercise is the hyperinsulinaemia which usually prevails in insulin treated patients [4, 5]. The most logical measure to prevent exercise induced hypoglycaemia in diabetic patients is to mimic the physiological reduction of insulin secretion occurring in non-diabetic subjects during exercise [6]. In patients with conventional insulin treatment this can be achieved by a drastic reduction of the insulin dose prior to or even after exercise as we [7] and others have

shown [8] previously. As a consequence, certain guidelines for prevention of exercise induced hypoglycaemia in patients on conventional insulin treatment have been proposed [6, 9].

In principle, patients with continuous subcutaneous insulin infusion (CSII) therapy should also follow guidelines such as reduction of the insulin bolus in anticipation of postprandial exercise [10] and adaptation of the insulin infusion rate [11]. However, most previous studies on exercise and CSII [12–16] were performed to compare the metabolic and hormonal effects of exercise in patients on CSII therapy rather than to investigate measures to prevent exercise induced metabolic complications. In order to estimate the insulin dose reduction necessary to prevent acute and/or late hypoglycaemic reactions in CSII treated Type 1 diabetic patients with (near)normoglycaemia, we have studied the effects of various basal insulin infusion rates both with and without a reduced premeal in-

Fig. 1. Diagram of five different experimental protocols (P_I–P_V) showing mealtime and modifications of exercise, basal insulin infusion rate (BR) and insulin bolus. (For further details see text)

sulin bolus on glucose homeostasis in a group of CSII treated diabetic patients performing exercise of a defined duration and intensity.

Subjects and methods

Subjects

Seven male, physically untrained, C-peptide negative Type 1 diabetic patients treated with CSII were recruited from our outpatient clinic and volunteered to participate in the study after giving their written informed consent. The study was approved by the Ethical Committee of the Medical Faculty of the University of Düsseldorf according to the Declaration of Helsinki. Further clinical and laboratory data are given in Table 1. Except for two patients with background retinopathy all patients were free of diabetic late complications as assessed by ophthalmoscopy, creatinine clearance, proteinuria and clinical examination. The patients were otherwise healthy and received no medication other than insulin. The patients had been on CSII treatment for 4 to 17 months and maintained normoglycaemia or near normoglycaemia as indicated by home blood glucose monitoring and HbA_{1c} levels (normal range 4.1–7.8%). The individual insulin doses are given in Table 1. Purified porcine regular insulin (Actrapid, Novo Industri, Copenhagen, Denmark) was infused using an Auto Syringe pump AS 6 C (Auto Syringe Inc., Hookset, New Hampshire, USA) via a 25 gauge metal tip catheter

(Venofix, Braun Melsungen, FRG) inserted into the subcutaneous tissue of the anterior abdominal wall in a way that excluded intramuscular infusion.

Experimental design

Each patient participated in five different protocols (P_I–P_V) with an interval of at least 10 days between each experiment. Insulin infusion rates and exercise were varied in the five protocols as shown in Figure 1, while all other conditions were kept constant. All subjects started with P_I which served as the control experiment with the usual insulin dose but without exercise. P_{II}–P_{IV} were performed in random order, in P_{II} the insulin rates were not changed and leg exercise was performed for 60 min on a cycle ergometer. In P_{III} and P_{IV} the basal insulin infusion rate was discontinued during exercise and thereafter, insulin was infused at 100% (P_{III}) and 50% (P_{IV}) of the initial basal rate until the end of the experiment. The results of the blood glucose concentrations obtained in these protocols led to the design of P_V. In this protocol the premeal insulin bolus was reduced by 50%, the basal rate was discontinued during exercise and insulin was infused at 75% of the initial rate during the post exercise period.

Experimental procedures

The patients reported to the laboratory at 07.30 hours after an overnight fast. Studies were initiated only if fasting blood glucose was in the normal range and no hypoglycaemic reactions had occurred during the preceding night. For this purpose the patients had to monitor blood glucose values at bed-time of the preceding day, at 03.00 hours, and on the morning of the experiment. On arrival in the laboratory a 17 gauge teflon cannula was inserted into an antecubital vein for blood sampling, and was kept patent by infusion of NaCl (154 mol/l). After 30 min of resting in a supine position and with drawal of basal blood samples the patients administered the usual premeal insulin bolus (50% in P_V). The insulin dose varied among patients but was identical for all protocols. The patients ate a standard breakfast 15 min later containing approximately 48 g carbohydrate, 20 g fat and 20 g protein. The meal was consumed over a 15 min period. Exercise was started 90 min after administration of the insulin bolus and continued for 60 min. The patients exercised on a vertical cycle ergometer (Conditronic 30, Keiper Dynavit, Rockenhausen, FRG) allowing continuous monitoring of pulse rate by a pulsemeter fixed to one ear lobe. On the basis of continuously adjusting to the preset pulse rate of 110 to 120 per min the patients performed a workload of an average of 80 watt. The workload did not differ between the five protocols and corresponded to a calculated O₂ intake of 1.3 l/min which can be classified as mild to moderate exercise intensity [17]. The subsequent post-exercise period was 5 h 30 min; thus the total experimental time span of each protocol was 8 h and 20 min. Before and after exercise the patients rested in a supine position. Except for breakfast all subjects abstained from

Table 1. Median and range of clinical data of seven Type 1 (insulin dependent) diabetic patients

Age (years)	20	(15–31)
Duration of diabetes (years)	9	(7–14)
Body mass index (kg/m ²)	22.1	(20.6–24.0)
Blood pressure (mm Hg)	120/80	(110/60–140/90)
Creatinine clearance (ml/min)	110	(90–125)
Proteinuria (mg/24 h)	40	(18–101)
HDL-cholesterol (mmol/l)	1.43	(1.17–1.72)
Triglyceride (mmol/l)	0.70	(0.53–0.97)
Insulin basal rate (U · kg ⁻¹ · 24 h)	0.32	(0.24–0.57)
Insulin bolus (U/10 g CHO)	1.4	(1.0–1.5)
HbA _{1c} (%)	7.3	(6.6–8.0)

Fig. 2. Blood glucose concentrations of continuous subcutaneous insulin infusion (CSII) treated Type 1 (insulin-dependent) diabetic patients before, during and after mild to moderate exercise in the five different protocols. Curved arrows indicate time and number of patients dropping out due to hypoglycaemia. Figures in brackets indicate number of patients continuing the protocol. Values are given as mean $\pm$ SEM indicated by vertical bars

food, caffeinated beverages and smoking throughout the experiment. An experiment was discontinued when blood glucose fell to 2.5 mmol/l or less. The discontinuation of the basal insulin infusion during exercise was achieved by removing the battery from the insulin pump.

Analytical procedures

Thirty minutes after the insertion of the intravenous cannula, blood samples were taken for base-line measurements at -20, -15 and 0 min. Thereafter, blood samples were taken every 15 min for instant blood glucose measurements, using the Beckman Glucose Analyzer (Beckman Instruments, Fullerton, Calif., USA). At intervals indicated in all Figures and Tables additional blood samples were collected into chilled tubes. One portion of whole blood was immediately added to ice-cold 2 N HClO₄, and the neutralized supernatant was assayed for pyruvate, acetoacetate and β -hydroxybutyrate as previously described [1]. Serum lactate was determined by an enzymatic-amperometric method [18]. Another portion of blood was transferred into chilled tubes containing EDTA-Na₂ and aprotinin. After centrifugation plasma was frozen at -20°C for later determi-

nation of glucagon by radioimmunoassay with use of 30K antiserum (kindly provided by Dr. R. Unger, Dallas, Tex USA). Plasma catecholamine levels were analysed by a radioenzymatic assay [19] from deproteinized plasma stored at -70°C. A fourth portion of the blood was centrifuged and the serum stored at -20°C for analysis of serum concentrations of non-esterified fatty acids [20], free insulin [21], growth hormone and cortisol [1].

Statistical analysis

Results are expressed as means $\pm$ SEM. For comparison within the same protocol, the paired *t*-test was used. Analysis of variance was used to compare the various test periods (base-line, meal, exercise and post-exercise) of the five protocols. Post hoc analysis for testing differences between two protocols was performed using the Duncan *t*-test.

Results

Blood glucose concentrations and serum free insulin levels

In the control protocol, mean base-line blood glucose concentration (Fig. 2) was 6.1 ± 0.2 mmol/l. After insulin bolus administration, it fell slightly and was followed by a postprandial increase reaching a maximum of 7.2 ± 0.7 mmol/l at 150 min. Thereafter, blood glucose declined continuously to a mean value of 4.3 ± 0.6 mmol/l at 480 min. Comparing the five protocols, no significant differences were observed in base-line blood glucose concentrations ($F(4,29) = 0.59$) and in mean values calculated over the postprandial period (15–90 min; $F(4,29) = 2.18$); however, the 90 min value in protocol P_V (9.0 ± 1.1 mmol/l) was significantly higher than in the other protocols ($F(1,29) = 2.31$; $p < 0.05$).

A substantial decrease in the blood glucose concentration was observed in all protocols during the second half of the exercise period. In protocol P_{II} four patients had to terminate exercise due to blood glucose values of 2.5 mmol/l or below. In the three patients who completed the protocol the blood glucose concentrations remained between 3.3 and 3.9 mmol/l until the end of the study. In protocol P_{III}, only two patients had to interrupt the study during exercise due to low blood glucose concentrations. After exercise, glycaemia of the remaining five patients first rose slightly to a maximal value of 6.2 ± 1.0 mmol/l at 270 min and, thereafter, decreased to 5.0 ± 0.7 mmol/l at 480 min. In protocol P_{IV}, again two patients developed hypoglycaemic values and had to interrupt exercise, whereas the post-exercise period of the remaining five patients who now received only 50% of their usual basal insulin infusion rate in accordance with the experimental protocol ended with a blood glucose increase to a maximum of 8.4 ± 1.2 mmol/l. Only in protocol P_V where the pre-meal insulin bolus – reduced by 50% – resulted in an elevated pre-exercise blood glucose level, no hypoglycaemia was observed. When a basal rate reduced by 25% was infused during the post-exercise period, glycaemia increased to 8.6 ± 1.2 mmol/l at 360 min and fell slightly toward 8.0 ± 0.9 mmol/l at the end of the protocol. During the post-exercise period, blood glucose concentrations were

Fig. 3. Serum free insulin concentrations of CSII treated Type 1 diabetic patients before, during and after mild to moderate exercise in the five different protocols. Symbols as in Fig. 2

significantly different between the four protocols P_{II} to P_V when the maximal levels of each protocol were compared ($F(3,15) = 3.55$, $p < 0.05$). These differences were mainly due to low blood glucose concentrations in P_{II} and elevated values in P_{IV} and P_V.

Under control conditions (P_I), the mean base-line concentration of serum free insulin was 89 ± 14.4 pmol/l (Fig. 3); 30 min after administration of the insulin bolus, an increase of insulin levels to a mean of 225 ± 25.8 pmol/l occurred which was followed by a plateau over 60 min and by a decrease to 146.5 ± 10.7 pmol/l at 180 min. Thereafter, mean serum free insulin fell slightly and consistently reaching nearly base-line concentrations at 480 min. Whereas no significant differences between the five protocols were obtained in base-line insulin levels ($F(4,29) = 0.65$), the increase after bolus administration was significantly different ($F(4,29) = 3.77$, $p < 0.05$) which was caused mainly by low values in P_V in accordance with the experimental protocol. In P_{II} the continuous administration of the basal insulin rate during exercise was associated with a further increase of serum free insulin in three out of six patients during the first 30 min of exercise. In those three patients who were able to continue exercise

without hypoglycaemia, serum insulin concentrations increased even further at a range two- to threefold higher than the base-line values until the end of the study. In protocol P_{III} and P_V, nearly identical values of free insulin were obtained after exercise when compared with the control protocol. The last 3 h of P_{IV} were characterized by low free insulin concentrations ranging between 36 and 59 pmol/l. Comparing the insulin concentrations of all five protocols, the analysis of variance revealed significant differences in maximal and mean concentrations between the protocols over the post-exercise period ($F(4,29) = 4.23$, and $F(4,29) = 5.40$, $p < 0.05$).

Metabolic variables

Mean postabsorptive blood concentrations of ketone bodies (acetoacetate and β -hydroxybutyrate; Table 2) were at 209 and 249 μ mol/l respectively in the control protocol and did not differ significantly from the values of P_{II} to P_V. After the insulin bolus and breakfast, a decrease

Table 2. Mean $\pm$ SEM blood concentrations of ketone bodies (acetoacetate plus β -hydroxybutyrate) expressed in μ mol/l

Time Min	P _I n = 7	P _{II} n = 7	P _{III} n = 7	P _{IV} n = 7	P _V n = 6
-15	249 $\pm$ 29	201 $\pm$ 53	297 $\pm$ 108	167 $\pm$ 29	298 $\pm$ 68
0	209 $\pm$ 20	221 $\pm$ 57	257 $\pm$ 91	176 $\pm$ 35	275 $\pm$ 68
30	141 $\pm$ 18	137 $\pm$ 19	176 $\pm$ 44	149 $\pm$ 15	237 $\pm$ 36
60	170 $\pm$ 29	154 $\pm$ 18	207 $\pm$ 16	181 $\pm$ 12	198 $\pm$ 40
90	133 $\pm$ 25	143 $\pm$ 20	167 $\pm$ 17	159 $\pm$ 17	200 $\pm$ 16
120	160 $\pm$ 21	143 $\pm$ 18 ^a	156 $\pm$ 25	190 $\pm$ 31 ^a	207 $\pm$ 17
150	169 $\pm$ 32	140 $\pm$ 21 ^c	212 $\pm$ 48 ^b	162 $\pm$ 17 ^b	217 $\pm$ 23
180	176 $\pm$ 44	137 $\pm$ 12	246 $\pm$ 111	174 $\pm$ 24	204 $\pm$ 29
210	177 $\pm$ 46	103 $\pm$ 22	234 $\pm$ 73	264 $\pm$ 65	230 $\pm$ 37
240	190 $\pm$ 62	130 $\pm$ 12	334 $\pm$ 65	374 $\pm$ 126	289 $\pm$ 56
300	161 $\pm$ 37	170 $\pm$ 38	452 $\pm$ 105	558 $\pm$ 178	384 $\pm$ 77
360	270 $\pm$ 93	203 $\pm$ 48	452 $\pm$ 118	556 $\pm$ 197	379 $\pm$ 65
420	361 $\pm$ 134	307 $\pm$ 127	530 $\pm$ 139	514 $\pm$ 102	375 $\pm$ 65
480	420 $\pm$ 167	397 $\pm$ 85	372 $\pm$ 112	472 $\pm$ 117	387 $\pm$ 51

^a 6; ^b 5; ^c 3 indicate time of drop outs and number of patients who finished the protocol

Table 3. Mean $\pm$ SEM serum concentrations of non-esterified free fatty acids (μ mol/l)

Time Min	P _I n = 7	P _{II} n = 7	P _{III} n = 7	P _{IV} n = 7	P _V n = 6
-15	665 $\pm$ 61	683 $\pm$ 83	653 $\pm$ 63	714 $\pm$ 101	743 $\pm$ 111
0	646 $\pm$ 64	620 $\pm$ 70	662 $\pm$ 74	707 $\pm$ 77	714 $\pm$ 118
30	603 $\pm$ 51	622 $\pm$ 73	636 $\pm$ 80	685 $\pm$ 66	704 $\pm$ 106
60	587 $\pm$ 63	553 $\pm$ 58	625 $\pm$ 82	670 $\pm$ 80	669 $\pm$ 75
90	608 $\pm$ 83	620 $\pm$ 78	582 $\pm$ 71	622 $\pm$ 73	773 $\pm$ 153
120	625 $\pm$ 98	617 $\pm$ 61 ^a	589 $\pm$ 52	656 $\pm$ 78 ^a	734 $\pm$ 109
150	692 $\pm$ 94	551 $\pm$ 66 ^c	515 $\pm$ 67 ^b	733 $\pm$ 122 ^b	670 $\pm$ 130
180	698 $\pm$ 109	525 $\pm$ 47	541 $\pm$ 68	775 $\pm$ 142	642 $\pm$ 123
210	671 $\pm$ 95	549 $\pm$ 87	612 $\pm$ 49	836 $\pm$ 184	797 $\pm$ 132
240	696 $\pm$ 91	572 $\pm$ 67	696 $\pm$ 41	969 $\pm$ 231	765 $\pm$ 127
300	777 $\pm$ 67	705 $\pm$ 70	738 $\pm$ 57	1558 $\pm$ 214	833 $\pm$ 164
360	781 $\pm$ 85	707 $\pm$ 21	676 $\pm$ 39	1059 $\pm$ 212	846 $\pm$ 170
420	786 $\pm$ 67	784 $\pm$ 124	697 $\pm$ 441	1001 $\pm$ 168	860 $\pm$ 175
480	927 $\pm$ 77	719 $\pm$ 111	710 $\pm$ 77	1165 $\pm$ 195	1012 $\pm$ 190

^a 6; ^b 5; ^c 3 indicate time of drop outs and number of patients who finished the protocol

Fig. 4. Plasma adrenaline and noradrenaline concentrations of CSII treated Type 1 diabetic patients before, during and after mild to moderate exercise in the five different protocols. Plasma epinephrine ■—■; plasma norepinephrine ●—●

of ketone body concentration was observed in all protocols. No significant changes were obtained during exercise and in the early post-exercise phase, from 240 min onwards, a consistent increase was seen similarly in all protocols. This increase was probably due to the ongoing abstinence from food by the subjects and was found to be most pronounced in protocol P_{IV} where in addition, the serum free insulin concentrations were in a low range.

Mean serum concentrations of non-esterified fatty acids (NEFA; Table 3) ranged between 620 and 714 $\mu\text{mol/l}$ during the base-line period of all the protocols. Following exercise NEFA increased consistently in all protocols, reaching significantly higher levels at 480 min as compared to base-line levels in P_I and P_V ($p < 0.01$, $p < 0.05$). Base-line values of mean blood concentrations of pyruvate ranged between 60 ± 10 and $80 \pm 9 \mu\text{mol/l}$ in the different protocols. The pattern of pyruvate levels, seen throughout all the exercise protocols, was characterized by increases to maximal values at 60 min followed by a steady decrease to base-line levels at 240 min without further change. Under resting conditions blood lactate concentrations ranged from 0.9 ± 0.1 to $1.1 \pm 0.1 \text{ mmol/l}$

and, increased significantly by comparable amounts during all exercise periods in accordance with the moderate work load applied.

Hormonal responses

No differences between the five protocols were seen in base-line plasma concentrations of either norepinephrine or epinephrine (Fig. 4). In P_I, the mean norepinephrine concentrations increased from 1.64 ± 0.25 to $2.4 \pm 0.2 \text{ nmol/l}$ ($p < 0.05$) within the first 30 min of the protocol and then returned to base-line levels at 90 min. The early increase of norepinephrine during the initial 30 min was similar in all protocols. During exercise norepinephrine rose further reaching maximal levels at 150 min and returned to base-line values thereafter. Plasma epinephrine concentrations starting at a mean of $442 \pm 65.5 \text{ pmol/l}$ remained virtually unchanged throughout P_I but rose during exercise reaching maximal values at 120 and 150 min. These increases, however, were less pronounced than those of norepinephrine levels.

Fig. 5. Serum growth hormone concentrations of CSII treated Type 1 diabetic patients before, during and after mild to moderate exercise in the five different protocols. Symbols as in Fig. 2

After an initial decrease from base-line (range: 4.3 to 6.3 µg/l) to 90 min values (range: 0.4 to 0.6 µg/l), mean serum growth hormone concentrations (Fig. 5) responded to exercise with an acute increase resulting in maximal values at the end of exercise (range: 8.2 to 11.9 µg/l). This increase was similar in P_{II} to P_V; thereafter, growth hormone concentrations declined to values in the range of 1.2 and 3.4 µg/l. Plasma glucagon and serum cortisol concentrations did not differ among protocols under basal conditions and did not increase during or after the exercise periods.

Discussion

This study was performed to find an estimate of the insulin dosage adjustments necessary to prevent exercise induced hypoglycaemia in stable, (near)normoglycaemic Type 1 diabetic patients treated with CSII. Their stable metabolic situation was documented by concentrations of metabolites and counterregulatory hormones being comparable to those of normal subjects [1, 22]. The nearly twofold rise of plasma norepinephrine and the less pronounced rise of

epinephrine during exercise were comparable to those observed in CSII-treated diabetic patients [23] and in non-diabetic individuals performing graded exercise [24]. As in normal subjects [1], serum growth hormone levels showed about an eightfold increase during exercise. These catecholamine and growth hormone responses are likely to be induced by exercise rather than by low blood glucose during exercise since the changes observed in P_V did not differ from those in the other protocols with lower levels of glycaemia. Mild to moderate exercise over 60 min was not associated with significant changes in plasma glucagon and serum cortisol concentrations indicating that one hour of moderate exercise does not stimulate secretion of these hormones.

The results of our study demonstrate that CSII-treated Type 1 diabetic patients at (near)normoglycaemia are likely to develop hypoglycaemia if they perform mild to moderate endurance exercise one hour after a meal without changing the insulin infusion rate and/or the premeal insulin bolus. This effect of exercise on blood glucose concentrations could be shown previously in CSII-treated patients [12–16]. However, as in normal subjects blood glucose levels appear to rise in Type 1 diabetic patients after a short bout of exercise as shown recently [25]. The hypoglycaemia in response to exercise varies partially depending on the intensity and duration of exercise, the alimentary status of the patients and the time interval between meal and exercise. As in the present study, a sharp fall in glycaemia was observed after 20 to 40 min of exercise started 90 min postprandially [12, 14]. When the patients began to exercise 2 or 3 h postprandially no significant decrease of blood glucose levels could be found [16]. Exercising in the fasting state led to a strong blood glucose lowering effect in CSII treated patients in one study [15] whereas under similar conditions no significant changes in blood glucose concentrations were seen by others [13]. In none of these studies was the possibility of reducing the basal and/or premeal insulin infusion rates to prevent hypoglycaemia during exercise considered. The need to reduce the insulin dose in association with exercise has been shown already in conventionally treated patients [4, 8] and is further emphasized by our observation that catecholamines and growth hormone responses to exercise were not sufficient to prevent the exercise induced hypoglycaemia. Also, no information has hitherto been provided regarding the occurrence of late hypoglycaemic reactions, since the post exercise observation periods were short (60–90 min) and extended to 150 min in one study only [16].

The present results show that the risk of exercise-induced hypoglycaemia can be reduced by discontinuing the basal insulin infusion rate during exercise. However, this measure did not totally prevent acute hypoglycaemia. Any hypoglycaemic reactions during exercise in these patients could be avoided by reducing the premeal insulin bolus in addition to interrupting the basal insulin infusion rate. After administration of the reduced insulin bolus the rise in serum free insulin levels was attenuated resulting in substantially lower serum insulin levels at the beginning of exercise as compared to all other conditions in this study. This reduced insulin concentration at the start of the exer-

cise was probably the main reason for the prevention of hypoglycaemia during exercise. It is even possible that solely the reduction of the premeal insulin bolus might have been sufficient to prevent hypoglycaemia during exercise in these patients. In daily life however, exercise may last longer than one hour and under such conditions it may be essential to stop the insulin infusion. In any case, patients planning to exercise within 1 to 2 h of a main meal for more than 30 min should be advised to take both precautions to prevent acute exercise induced hypoglycaemia, i.e. reduce the premeal bolus and interrupt the basal insulin infusion rate for the exercise period. If patients decide spontaneously to exercise within 1 to 2 h of a meal and administration of the insulin bolus, they still have the possibility of interrupting the insulin infusion to reduce the risk of hypoglycaemia. Under this condition hypoglycaemia during exercise may be prevented by consumption of additional amounts of carbohydrate prior to and/or during the physical activity.

Late-onset hypoglycaemic reactions after physical activity are not uncommon in tightly controlled diabetic patients [26, 27], as the enhancement of insulin sensitivity extends beyond the exercise period [28]. Exercise performed during late afternoon or evening hours carries a particular risk of nocturnal hypoglycaemia. Therefore, we have studied the effects of various basal insulin infusion rates for a period of 5 h 30 min after termination of the exercise. The infusion of the usually applied 100% basal rate after exercise was associated with blood glucose levels between 3.3 and 3.9 mmol/l and high free insulin levels in those three patients who were able to finish the study without hypoglycaemia. When interrupted during the exercise period, this insulin infusion rate was associated with normoglycaemia during the early post exercise period, while blood glucose tended to fall towards the end of the post-exercise period. The latter observation seems to be of particular importance if physical activity is performed during evening hours, which is likely to be the case with many patients. As a consequence low blood glucose levels and even hypoglycaemia must be expected during the night if the insulin infusion rate is not changed after exercise. A reduction of the basal insulin infusion rate by 25% after exercise was associated with stable near normoglycaemia while a more pronounced reduction of the infusion rate resulted in an undesirable deterioration of metabolic control.

In conclusion, Type 1 diabetic patients treated with continuous subcutaneous insulin infusion at (near)normoglycaemia need to reduce their insulin dosage before during and after mild to moderate endurance exercise in order to minimize the risk of acute and late hypoglycaemia. This recommendation should provide guidelines to guarantee the safety of CSII-treated subjects undertaking spontaneous physical activity during their everyday life.

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References

- Berger M, Berchtold P, Cüppers HJ, Drost H, Kley HK, Müller WA, Wiegmann W, Zimmermann-Telschow H, Gries FA, Krüskemper HL, Zimmermann H (1977) Metabolic and hormonal effects of muscular exercise in juvenile type diabetics *Diabetologia* 13: 355–365
- Vranic M, Berger M (1979) Exercise and diabetes mellitus. *Diabetes* 28: 147–167
- Richter EA, Galbo H (1986) Diabetes, insulin and exercise. *Sports Med* 3: 275–288
- Kemmer FW, Berchtold P, Berger M, Starke A, Cüppers HJ, Gries FA, Zimmermann H (1979) Exercise induced fall of blood glucose in insulin treated diabetics unrelated to alteration of insulin mobilization. *Diabetes* 28: 1131–1137
- Koivisto V, Felig P (1978) Effects of leg exercise on insulin absorption in diabetic patients. *N Engl J Med* 298: 77–83
- Kemmer FW, Berger M (1983) Exercise and Diabetes Mellitus: Physical activity as a part of daily life and its role in the treatment of diabetic patients. *Intern J Sports Med* 4: 77–88
- Kemmer FW, Sonnenberg GE, Cüppers HJ, Berger M (1986) Prevention of exercise induced hypoglycaemia in diabetes. In: Serrano-Rios M, Lefebvre PJ (eds) *Diabetes 1985*. Elsevier Amsterdam, pp 963–967
- Sane T, Helve E, Pelkonen R, Koivisto VA (1988) The adjustment of diet insulin dose during long-term endurance exercise in Type 1 (insulin-dependent) diabetic men. *Diabetologia* 31: 35–40
- Kemmer FW (1990) Exercise in diabetic patients. In: Torg JS, Welsh RP, Shepard RJ (eds) *Current therapy in sports medicine*, 2. Decker, Toronto, pp 109–114
- Schiffrin A, Parikh S (1985) Accommodating planned exercise in Type I diabetic patients on intensive treatment. *Diabetes Care* 8: 337–342
- Poussier P, Zinman B, Marliss EB, Albisser M, Perlman K, Caron D (1983) Open-loop intravenous insulin waveforms for postprandial exercise in Type I Diabetes. *Diabetes Care* 6: 129–134
- Koivisto V, Tronier B (1983) Postprandial blood glucose response to exercise in Type I diabetes: comparison between pump and injection therapy. *Diabetes Care* 6: 436–440
- Gooch BR, Abumrad NN, Robinson RP, Petrik M, Campbell D, Crofford OB (1983) Exercise in insulin-dependent diabetes mellitus: the effect of continuous insulin infusion using the subcutaneous, intravenous and intraperitoneal sites. *Diabetes Care* 6: 122–128
- Viberti GC, Home PD, Bilous RW, Alberti KGMM, Dalton N, Keen H, Pickup JC (1984) Metabolic effects of physical exercise in insulin-dependent diabetics controlled by continuous subcutaneous insulin infusion or conventional insulin therapy. *Acta Endocrinol* 105: 515–520
- Schiffrin A, Parikh S, Marliss EB, Desrosiers MM (1984) Metabolic response to fasting exercise in adolescent insulin-dependent diabetic subjects treated with continuous subcutaneous insulin infusion and intensive conventional therapy. *Diabetes Care* 7: 255–260
- Trovati M, Carta Q, Cavalot F, Vitali S, Passarino G, Rocca G, Emanuelli G, Lenti G (1984) Continuous subcutaneous insulin infusion and postprandial exercise in tightly controlled Type I (insulin dependent) diabetic patients. *Diabetes Care* 7: 327–330
- Jones NL, Campbell EJM (1982) *Clinical exercise testing*, 2nd edn. Saunders, Philadelphia
- Hochella NJ (1974) L-lactate. Determination with automatic analysers. In: Bergmeyer HU (ed) *Methods of enzymatic analysis*, 2nd edn. Verlag Chemie, Weinheim; Academic Press, New York London, pp 1479–1483

19. Sole MJ, Hussain MN (1977) A simple specific radioenzymatic assay for the simultaneous measurement of picogram quantities of norepinephrine, epinephrine and dopamine in plasma and tissues. *Biochem Med* 18: 301–307
20. McGee J, Allen KG (1974) Preparation of methyl esters from the saponifiable fatty acids in small biological specimens for gas-liquid chromatographic analysis. *J Chromatogr* 100: 35–42
21. Nakagawa S, Nakayama H, Sasaki T, Yoshino K, Yu Y, Shinozaki K, Aoki S, Mashimo K (1973) A simple method for determination of serum free insulin levels in insulin-treated patients. *Diabetes* 22: 590–600
22. Kemmer FW, Bisping R, Steingrüber HJ, Baar H, Hardtmann F, Schlaghecke R, Berger M (1986) Psychological stress and metabolic control in patients with Type I diabetes mellitus. *N Engl J Med* 314: 1078–1084
23. Tamborlane WV, Sherwin RS, Koivisto V, Hendler R, Genel M, Felig P (1979) Normalization of the growth hormone and catecholamine response to exercise in juvenile-onset diabetic subjects treated with a portable insulin infusion pump. *Diabetes* 28: 785–788
24. Galbo H, Holst JJ, Christensen NJ (1975) Glucagon and plasma catecholamine response to graded and prolonged exercise in man. *J Appl Physiol* 38: 70–76
25. Mitchell TH, Gebrehiwot A, Schiffrin A, Leiter LA, Marliss EB (1988) Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion. *Diabetes Care* 11: 311–317
26. Campaigne BN, Wallberg-Henriksson H, Gunnarsson R (1987) Glucose and Insulin response in relation to insulin dose and caloric intake 12 h after acute physical exercise in men with IDDM. *Diabetes Care* 10: 716–721
27. MacDonald MJ (1987) Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. *Diabetes Care* 10: 584–588
28. Bogardus C, Thuillez P, Ravussin E, Vasquez B, Narimiga M, Azhar S (1983) Effect of muscle glycogen depletion on in vivo insulin action in man. *J Clin Invest* 72: 1605–1610

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