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Metabolic and Hormonal Effects of Muscular Exercise in Juvenile Type Diabetics

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Summary. Metabolic and hormonal effects of muscular exercise were studied in juvenile-type diabetics in relation to the prevailing degree of metabolic control and compared with those in healthy control subjects. Two groups of diabetic patients, one in moderate metabolic control and one in ketosis due to insulin withdrawal, were subjected to a 3 hour bicycle ergometer test of comparable, mild work intensity. In both groups of diabetics the exercise-induced rise in blood lactate was similar, but was significantly higher than in control subjects. Blood alanine levels showed a transient, significant rise in both diabetic groups, but not in controls. Blood concentrations of branch-chained amino acids remained unchanged. In the moderately controlled diabetics, exercise induced a marked fall of blood glucose and increases in blood levels of free fatty acids (FFA), ketone bodies and glucagon, which were comparable to the exercise effects in normal controls. In ketotic diabetics, however, exercise led to an additional rise in blood glucose concentration and to increases in ketone body, glucagon and cortisol levels. Significant correlations were found between the exercise effect on blood glucose and initial blood levels of glucose, FFA, ketone bodies and branch chained amino acids: pre-exercise values of above 325 mg/dl glucose, 1173 μmol/l FFA, 2.13 mmol/l ketone bodies and 0.74 mmol/l branch chained amino acids led to increased blood glucose levels on exercise, whereas below these limits glucose fell during the exercise test. These findings seem to be, at least in part, explained by the hypothesis of a permissive effect of insulin during stimulation of muscle glucose uptake by exercise. The increased circulating levels of glucagon and cortisol during exercise in ketotic diabetics might represent additional hyperglycaemic and, probably more important, lipolytic and ketogenic stimuli. The results suggest that in moderately controlled, non-ketotic diabetics blood glucose falls during exercise; in ketotic, relatively insulin deficient patients, muscular activity has adverse metabolic and hormonal effects: a further increase in blood glucose, plasma glucagon and cortisol and a rapid aggravation of ketosis.

Key words: Juvenile type diabetes, muscular exercise, blood glucose, ketosis, free fatty acids, amino acids, insulin, glucagon, growth hormone, cortisol.

The importance of physical activity in the treatment of diabetes mellitus is generally acknowledged [33, 34], mainly because of its potential blood glucose lowering [33, 34, 36, 43] and insulin sparing [34] effects. On the other hand, clinical experience and anecdotal reports [3, 5, 13, 33, 20, 41, 47, 51] have indicated that in ketotic diabetics muscular exercise may have adverse and clinically deleterious metabolic consequences. The precise nature as well as the underlying pathophysiological mechanism of these conflicting observations remain, however, to be clarified. The aim of this study was to investigate comprehensively the metabolic and hormonal effects of prolonged mild muscular exercise in relation to the degree of metabolic control in juvenile diabetes.

Preliminary data of this study have been presented [7, 8].

Methods

Subjects

11 male patients with long-standing juvenile type diabetes and 6 healthy control subjects were studied at the Department of Medicine, University of Düs-

Table 1. Clinical data of patients and controls, and laboratory data at onset of the exercise test (mean values ± SEM; ranges are given in parentheses)

		Diabetic patients	
	Normal controls (n = 6)	In "moderate control" (n = 6)	Ketotic (n = 9)
Age (years)	31±2 (21–33)	29±2 (17–33)	28±2 (22–33)
Height (cm)	183±2 (176–188)	174±3 (165–186)	173±2 (167–186)
Weight (kg)	74±4 (59–86)	67±4 (55–77)	66±3 (59–77)
Relative weight (Broca's Index)*	−10±2 (−19–−2)	−11±3 (−19–+3)	−9±2 (−19–+3)
Duration of diabetes (yrs)	–	16±4 (4–31)	16±2 (4–31)
Current insulin dose (units/day)		60±6 (40–80)	55±4 (44–80)
Blood glucose (mg/dl)	73±3 (65–85)	184±18 (130–236)[a]	332±15 (273–414)[ab]
Serum FFA (μmol/l)	519±44 (394–681)	638±77 (397–899)	1125±82 (834–1592)[ab]
Serum glycerol (μmol/l)	46±5 (31–62)	53±12 (18–81)	111±12 (45–171)[ab]
Serum triglycerides (mg/dl)	103±23 (29–172)	99±27 (58–234)	173±20 (112–299)[ab]
Blood lactate (mmol/l)	0.83±0.16 (0.42–1.35)	0.78±0.08 (0.54–1.05)	1.04±0.08 (0.62–1.35)
Blood pyruvate (mmol/l)	0.07±0.01 (0.05–0.11)	0.05±0.01 (0.02–0.09)	0.09±0.02 (0.06–0.13)
Blood ketone bodies (mmol/l)	0.20±0.01 (0.18–0.22)	0.32±0.07 (0.13–0.59)	1.94±0.26 (1.06–3.51)[ab]
Blood branched chain amino acids (valine, leucine, isoleucine) (mmol/l)	0.46±0.03 (0.41–0.58)	0.46±0.05 (0.36–0.66)	0.78±0.07 (0.59–1.19)[ab]
Blood urea (mmol/l)	5.17±0.48 (3.17–6.49)	6.50±0.52 (3.97–7.61)	6.04±0.65 (3.93–8.87)
Blood pH	7.39±0.01 (7.38–7.42)	7.39±0.02 (7.36–7.48)	7.37±0.01 (7.33–7.42)
Blood HCO_3^- (meq/l)	22±1 (20–23)	23±1 (21–28)	21±1 (17–25)[b]
Haematocrit (%)	41±1 (38–45)	44±2 (38–49)	42±1 (37–46)

* Broca-Index $= \frac{\text{weight in kg} \times 100}{\text{height in cm} - 100} - 100$

[a] = value significantly different from normal controls at $p < 0.05$

[b] = value significantly different from diabetic patients in "moderate control" at $p < 0.05$

seldorf. The diabetics were controlled as in-patients in a metabolic ward on a weight maintaining diet (40–50% of the total caloric intake were given as carbohydrate, 15–20% as protein) for at least one week before the exercise test. The control subjects were hospital employees who were asked not to change their usual eating habits for two weeks prior to the exercise test; during this time their weights were constant.

Clinical data are given in Table 1. The patients were free of acute or chronic infectious diseases, cardiovascular disease, renal insufficiency (normal blood levels of urea and creatinine; no pathological proteinuria) and proliferative retinopathy. None of the subjects participated in competitive or other strenuous exercise on a regular basis.

The diabetic patients were on treatment with two daily injections of an intermediate acting insulin preparation, i.e. Depot Insulin® HOECHST or Semilente® insulin NOVO.

The diabetic patients were pretreated according to two protocols: one group of patients, described as diabetics in "moderate control", was given only 2/3 of their usual evening insulin dose at 18.00 hrs on the preceding day. At the onset of the exercise test, these patients were in moderate metabolic control (Table 1). In the second group, described as "ketotic diabetics", insulin was withheld for 18–48 hours (dependent on their individual metabolic stability) in order to induce a state of insulin-deficiency; at the onset of the exercise test, these patients were all in diabetic ketosis (Table 1); four patients were studied twice, i.e. according to the conditions of either group, at least three days apart.

Exercise Tests

The exercise tests were started at 08.00 hrs following an overnight fast of 12 to 14 hours. A teflon catheter was inserted into an antecubital vein, and kept patent by infusion with 0.154 mol/l saline. The patients were studied at rest and during exercise on a bicycle ergometer, in an upright position; following the workload blood samples were drawn while the patient rested in a supine position. The individuals were subjected to mild exercise for 180 min.

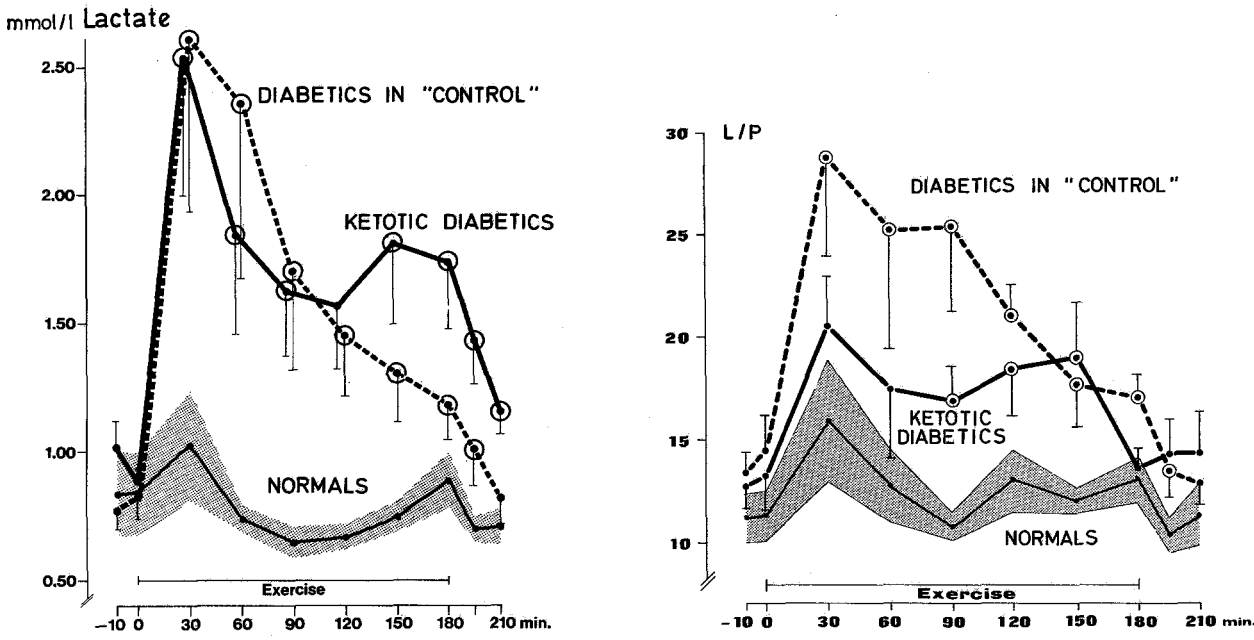

Fig. 1. Effect of prolonged exercise on blood lactate levels and lactate/pyruvate ratios (L/P) in healthy control subjects (Normals), diabetic patients in "moderate control" (Diabetics In "Control") and ketotic diabetic patients (Ketotic Diabetics). See Methods section for further details. Encircled values are significantly different from corresponding values of the control group at $p < 0.05$. The shaded area indicates the SEM of the mean values of the controls

Heart rate and ECG were continuously monitored using a conventional oscillograph; blood pressure was measured at repeated intervals during and after exercise. In order to apply an identical relative exercise intensity to each subject, the workload was adjusted to maintain a heart rate of approximately 110 beats/min. In all cases steady state conditions between heart rate and workload were reached at 70±15 (SD) watts corresponding to approximately 30–40% of the subjects' maximal work capacity. There were no significant differences in the workloads employed at a heart rate of 110 beats/min between the three different experimental groups. The ergometer test represented a severe physical or psychological stress to none of the subjects. Blood gas analyses were performed on capillary blood obtained from the ear lobe. Metabolic and hormonal variables were measured in blood samples drawn from the antecubital vein, without interruption of exercise, at indicated intervals (Figs. 1–4).

Processing of Blood Samples

Venous blood samples were immediately transferred into several chilled tubes: one portion was put into perchloric acid for deproteinization [32] and the neutralized supernatant was assayed for pyruvate, lactate, 3-hydroxybutyrate and acetoacetate on the same day; an aliquot of the supernatant was frozen for subsequent analysis of amino acid and urea levels. Another portion was transferred into tubes containing EDTA-Na_2 and Trasylol®, centrifuged, and plasma samples were frozen for subsequent analysis of glucagon levels. From a third portion of blood, serum was obtained for analysis of triglyceride, glycerol and free fatty acid levels which were done on the same day; the remainder of the serum was frozen in separate portions for subsequent radioimmunological hormone assays. Additional portions of whole blood were processed for determinations of glucose concentrations and haematocrit.

Analytical Methods

Glucose was analyzed in whole blood by the method of Grady and Lamar [28], using a Technicon autoanalyser. Lactate [32], pyruvate [12], 3-hydroxybutyrate [61], acetoacetate [42] were determined in whole blood using enzymatic techniques. Glycerol [19] and triglycerides [19] were measured in serum enzymatically and serum free fatty acids (FFA) colorimetrically according to the method of Dole and Meinertz [18] as modified by Lochner and Nasseri [40].

Individual amino acids and urea were measured in deproteinized extracts of whole blood using a Biotronik amino-acid analyzer. With the separation techniques employed glutathione did not interfere with the determinations of the reported amino acids.

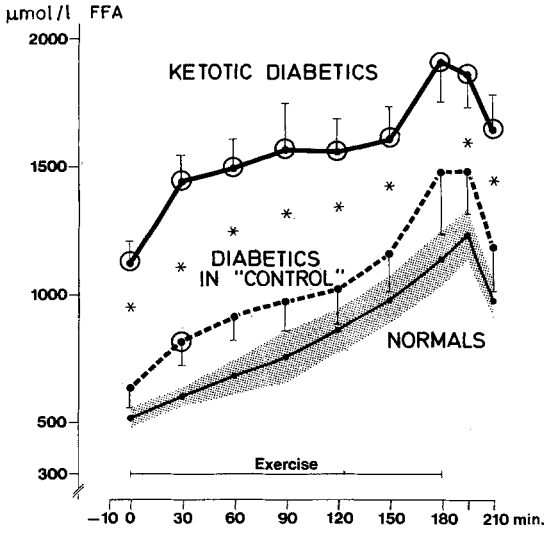

Fig. 2. Effect of prolonged exercise on serum levels of FFA. Symbols as in Figure 1. Stars indicate statistically significant differences between the corresponding values of the two groups of diabetic patients at $p < 0.05$

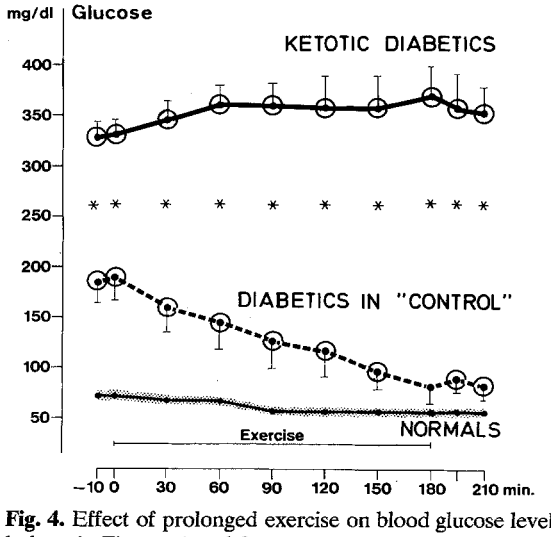

Fig. 4. Effect of prolonged exercise on blood glucose levels. Symbols as in Figures 1 and 2

Routine laboratory procedures were used to measure the haematocrit (microcapillary haematocrit centrifuge) and blood gas concentrations (automatic blood gas analyzer, AVL Company, Graz, Austria). Serum levels of growth hormone [60], cortisol [37] and plasma glucagon [45, 56] concentrations (using the glucagon antiserum 30-K) were determined by radioimmunoassay. For the radioimmunoassay of insulin a solid-phase method (Phadebas Insulin Test, Pharmacia Co., Uppsala, Sweden) was used [59].

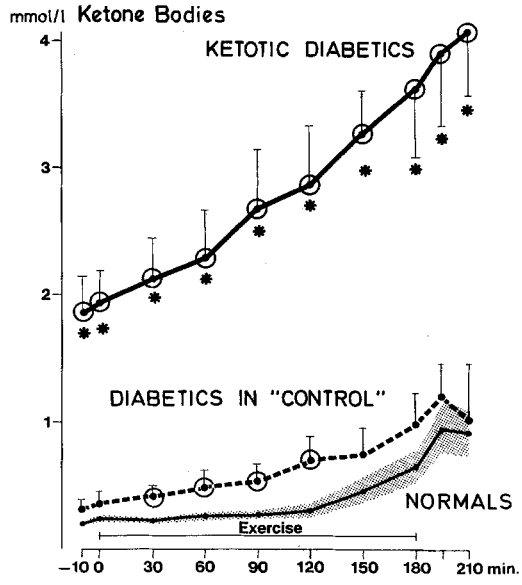

Fig. 3. Effect of prolonged exercise on blood levels of ketone bodies. Symbols as in Figures 1 and 2

Calculations and Statistical Methods

"Ketone body" concentration refers to the sum of whole blood concentrations of 3-hydroxybutyrate and acetoacetate and "branched-chain amino acids" concentration to the sum of whole blood levels of valine, leucine and isoleucine.

Data in the text, tables and figures are given as means ± SEM. Standard statistical methods have been employed using the unpaired Student t-test, unless otherwise indicated.

Results

Urea, Haematocrit, pH, HCO_3^-, Lactate and Pyruvate

In none of the three experimental groups was a significant change of haematocrit, pH, HCO_3^- or urea observed during or after the exercise period. The mild intensity of the endurance exercise employed in this study is also demonstrated by the relatively minor increases in blood lactate concentrations and lactate/pyruvate ratios (Fig. 1). During the entire exercise period, in both groups of patients, blood lactate concentrations and lactate/pyruvate ratios were significantly higher than in the controls, except in ketotic diabetics at 30, 60 and 180 min. Both lactate levels and lactate/pyruvate ratios showed no significant differences at any time point when the two groups of diabetic patients were compared.

Table 2. Effect of prolonged exercise on blood levels of amino acids (N = normal controls; n = 5; Dc = diabetics in "moderate control", n = 4; Dk = ketotic diabetic, n = 5)

		Basal concentration[1]	Exercise			30′ after exercise
			60′	120′	180′	
Arginine	N	78±4	67±6	77±6	72±2	75±6
(μmmol/l)	Dc	68±11	59±11	77±16	59±11	52±14
	Dk	67±6	59±6	62±2	49±2[ba]	46±4[ba]
Glycine	N	0.32±0.02	0.29±0.01	0.32±0.03	0.28±0.02	0.26±0.02[a]
(mmol/l)	Dc	0.38±0.04	0.36±0.01[b]	0.38±0.05	0.33±0.02	0.33±0.05
	Dk	0.31±0.02	0.31±0.02	0.31±0.02	0.27±0.03	0.27±0.02
Alanine	N	0.32±0.02	0.32±0.03	0.30±0.03	0.27±0.01[a]	0.24±0.03[a]
(mmol/l)	Dc	0.28±0.02	0.35±0.02[a]	0.36±0.03[a]	0.28±0.02	0.26±0.02
	Dk	0.33±0.03	0.38±0.03	0.40±0.02[ba]	0.33±0.03	0.34±0.04
Valine	N	0.25±0.02	0.23±0.03	0.23±0.01	0.22±0.01	0.22±0.02
(mmol/l)	Dc	0.24±0.03	0.25±0.04	0.27±0.05	0.20±0.02	0.21±0.02
	Dk	0.40±0.06[bc]	0.37±0.05[bc]	0.39±0.06[bc]	0.35±0.07[bc]	0.37±0.05[bc]
Leucine	N	0.14±0.01	0.12±0.01	0.13±0.01	0.12±0.01	0.12±0.01
(mmol/l)	Dc	0.14±0.03	0.14±0.04	0.14±0.03	0.11±0.02	0.12±0.01
	Dk	0.27±0.05[bc]	0.27±0.04[bc]	0.25±0.05[bc]	0.22±0.05[bc]	0.23±0.04[bc]
Isoleucine	N	0.07±0.01	0.06±0.01	0.06±0.01	0.06±0.01	0.05±0.01
(mmol/l)	Dc	0.08±0.02	0.07±0.02	0.07±0.01	0.05±0.01	0.06±0.01
	Dk	0.14±0.02[bc]	0.12±0.03[bc]	0.12±0.02[bc]	0.11±0.02[bc]	0.12±0.02[bc]
Tyrosine	N	59±6	56±6	57±6	59±4	53±4
(μmol/l)	Dc	54±8	55±5	59±4	49±5	51±10
	Dk	59±4	58±2	60±3	51±5	56±6
Penylalanine	N	52±4	45±4	46±4	44±1[a]	41±1[a]
(μmol/l)	Dc	53±4	52±4	54±7	51±4	49±5
	Dk	57±5	53±3[b]	57±3[b]	53±5	55±4[b]
Lysine	N	0.18±0.01	0.16±0.01	0.17±0.01	0.16±0.01	0.16±0.01
(mmol/l)	Dc	0.17±0.01	0.16±0.02	0.18±0.03	0.15±0.02	0.16±0.01
	Dk	0.17±0.02	0.16±0.02	0.16±0.01	0.15±0.02	0.15±0.01
Ornithine	N	87±5	78±8	79±4	75±6	71±4
(μmol/l)	Dc	79±10	76±10	79±15	68±5	69±6
	Dk	80±9	77±9	77±6	72±10	67±6
Histidine	N	97±8	92±10	85±8	87±3	82±9
(μmol/l)	Dc	84±4	78±5	84±11	72±7	74±6
	Dk	83±5	87±8	94±12	86±7	92±6

[1] mean of two determinations at −10′ and 0′
[a] significantly different as compared to basal at $p < 0.05$
[b] significantly different from corresponding value of the control group at $p < 0.05$
[c] significantly different from corresponding value of the group Dc at $p < 0.05$

Free Fatty Acids (Fig. 2)

FFA levels exhibited a continuous rise in response to exercise, resulting in an increment of approximately 600 μmol FFA/l in all three groups. The ketotic patients showed significantly elevated free fatty acid concentrations at all times measured. Serum glycerol concentrations showed a comparable behaviour to the FFA in all three groups (data not shown).

Ketone Bodies (Fig. 3)

Blood ketone body concentrations at rest were almost 10-fold increased in ketotic patients when compared with healthy individuals. For the diabetics in "moderate control" and the control group, blood ketone bodies showed a gradual increase: only after 150 min of exercise were ketone body concentrations significantly ($p < 0.05$ using a paired t-test) elevated when compared with basal levels in both groups. In contrast, exercise induced a rapid, early increase in ketone body levels, in ketotic patients ($p < 0.05$ at 60 min using a paired t-test). All three groups exhibited a continuing rise of ketone bodies after cessation of exercise; this phenomenon was particularly apparent in the ketotic patients, in whom a final mean ketone body concentration of approximately 4 mmol/l was observed.

Amino Acids (Table 2)

Alanine concentrations which were comparable in the three groups before exercise rose transiently af-

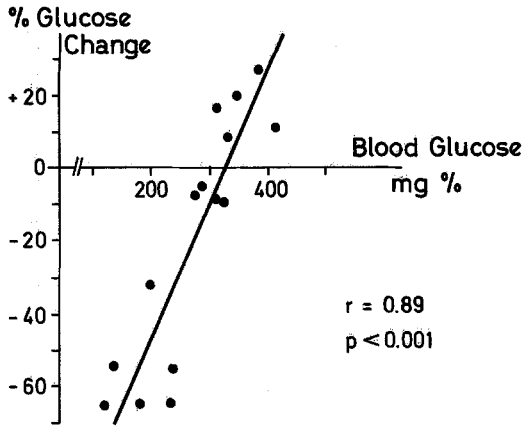

Fig. 5. Correlation between change of blood glucose induced by 180 minutes of exercise expressed in percent of initial blood glucose levels (y axis) and initial blood glucose concentrations in mg/dl (x axis)

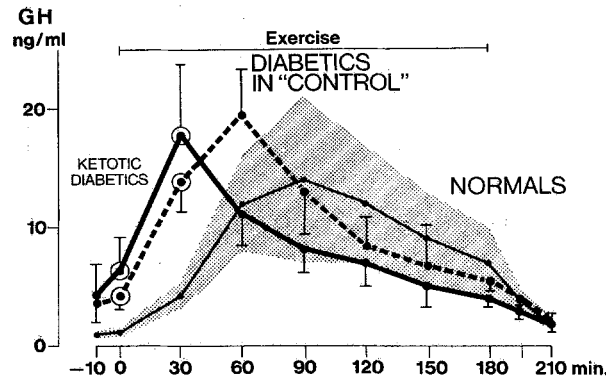

Fig. 6. Effect of prolonged exercise on serum growth-hormone (GH) levels. Symbols as in Figures 1 and 2

Table 3. Correlations between change in blood glucose (per cent of initial value) during exercise and initial metabolic variables in patients with juvenile type diabetes (n = 15)

x	y	Correlation equation	Intercept with the abscissa	r	t
Initial blood levels of					
glucose (mg/dl)	Change of	$y = -117+0.36x$	325	0.89	6.69
FFA (mmol/l)	blood glucose	$y = -90+76.7x$	1.173	0.73	3.85
ketone bodies (mmol/l)	expressed as	$y = -47+22.1x$	2.13	0.78	3.36
branched-chain amino acids (mmol/l)	per cent of initial value	$y = -73+98.1x$	0.74	0.66	3.07

ter 60 and 120 min of exercise in both groups of patients; in the controls, a significant fall at the end of, and 30 min after, the exercise test was observed. Blood levels of branched-chain amino acids were increased 1.5 to 2-fold in the ketotic diabetics compared with the two other groups.

In neither group was a significant effect of exercise on branched-chain amino acid levels observed. Arginine levels fell significantly towards the end of the exercise period in ketotic diabetics and so did phenylalanine in the control group. Glycine levels were significantly decreased in the control group 30 min after cessation of exercise. The concentrations of all other amino acids determined showed no significant changes (Table 2) and accordingly, blood levels of amino acids at 30, 90 and 150 min, as well as 15 min after cessation of exercise, which are not shown, did not reveal any additional significant information.

Blood Glucose (Fig. 4)

At all measured time points blood glucose concentrations were significantly different between the three experimental groups (except for the 180 min value in the control groups and the patients in "moderate control").

Blood glucose levels in the control group and the diabetic patients in "moderate control" fell during endurance exercise; on paired comparison this fall of blood glucose was already significant ($p < 0.05$) after 60 and 30 min of exercise, respectively. In ketotic diabetics exercise induced a rise in blood glucose; on paired comparison this increase in blood glucose levels was statistically significant 30, 60 and 90 min ($p < 0.05$) after the onset of exercise.

For a more detailed analysis of the data, the results of all 15 exercise experiments in patients with diabetes mellitus were pooled: a significant correlation was found between initial blood glucose concentrations and the change of blood glucose due to exercise (expressed as % of basal glycaemia) (Fig. 5). Above an initial fasting blood glucose concentration of 325 mg/dl exercise induced a further rise of blood glucose and below this level blood glucose concentrations decreased during the exercise test. In addition, the changes of blood glucose (expressed as percentage of initial glycaemia) were significantly correlated with the basal blood concentrations of free fatty acids, ketone bodies and branched

chain amino acids (Table 3): above initial levels of 1173 μmol/l FFA, 2.13 mmol/l ketone bodies and 0.74 mmol/l branched chain amino acids, exercise led to a rise; below these concentrations exercise induced a fall in blood glucose.

Insulin

In normal controls exercise induced a fall of serum insulin levels from 10±2 μU/ml at rest to 6±1 μU/ml at 180 min; during the entire exercise period insulin concentrations were significantly decreased ($p < 0.01$ using a paired t-test). No attempt was made to determine serum insulin levels in the diabetic patients because of the presence of insulin antibodies.

Growth Hormone (GH) (Fig. 6)

Basal serum GH levels in both groups of diabetics were significantly higher than in the controls ($p < 0.05$). In response to exercise, serum GH rose earlier in ketotic diabetics than in diabetics in "moderate control" and control subjects; at 30 min GH levels were significantly higher in both groups of diabetics compared to the controls (Fig. 6).

Glucagon (Fig. 7)

At rest, during exercise and thereafter plasma glucagon levels were consistently higher in ketotic diabetics than in the control subjects. In response to exercise, the ketotic diabetics showed a rapid and sharp elevation of glucagon levels in contrast to the much slower increases in diabetics in "moderate control" and control subjects. However, in all three groups the glucagon levels were significantly elevated at 150 and 180 min compared to basal values ($p < 0.05$, paired t-test). A simple correlation between mean glucagon levels and mean ketone body concentrations of each group was demonstrable ($n = 30$, $r = 0.85$, $p < 0.001$). In addition, there was a correlation between mean glucagon levels and mean FFA levels ($n = 30$, $r = 0.8$, $p < 0.001$).

Cortisol (Fig. 8)

Basal serum cortisol levels were not different in the three groups. Both in controls and in diabetic patients in "moderate control" exercise did not induce any significant changes in cortisol levels. By contrast, in ketotic diabetics serum cortisol concentrations rose significantly during exercise, reaching a peak level at 180 min; in ketotic diabetics serum

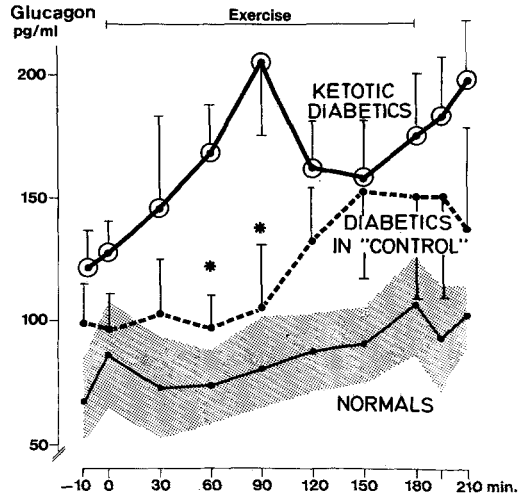

Fig. 7. Effect of prolonged exercise on plasma glucagon levels. Symbols as in Figures 1 and 2

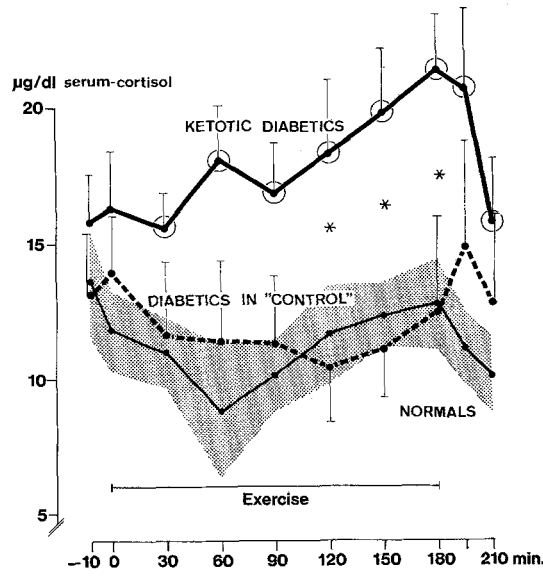

Fig. 8. Effect of prolonged exercise on serum cortisol levels. Symbols as in Figures 1 and 2

cortisol levels were significantly higher than in control subjects during the entire exercise period and thereafter and significantly higher than in diabetics in "moderate control" from 120 to 180 min.

Discussion

The results of this study demonstrate that the hormonal and metabolic effects of mild prolonged exercise in juvenile-type diabetes are dependent on the patients' state of metabolic control. In particular, exercise induced a fall of blood glucose in patients in moderate metabolic control, but a further rise of glucose levels in ketotic diabetics.

The possibility that these findings have been caused by differences in the intensity of the exercise is highly unlikely. There were no significant differences in the absolute or the relative workloads between the experimental groups. Major differences in the status of training were ruled out. It has been suggested that the metabolic effects of exercise in diabetics can be masked by an increased mobilization of subcutaneously injected insulin induced by the contractions and/or concomitant circulatory changes [6, 35, 46]. Hence, in previous investigations, a distinction between the genuine metabolic effects of exercise and a possible exercise – induced potentiation of injected insulin was impossible [13, 38, 41]. In this study injections of intermediate acting insulin were withdrawn for at least 14 hours, a time interval after which the persistence of significant amounts of mobilizable insulin at the subcutaneous site can be excluded [11]. The instantaneous and steep rise of serum FFA in all the diabetics of this study lends further support to the argument that mobilization of insulin during exercise did not occur [46]. But, in the diabetics in "moderate control" blood levels of metabolites – except for the moderate hyperglycaemia – were within the normal range indicating that systemic insulin was still present in effective amounts. By contrast, in the ketotic diabetics the prolonged insulin withdrawal had induced a considerable degree of insulin deficiency which manifested itself in sizeable elevations of blood glucose, ketone bodies, FFA, glycerol, triglyceride and branch chained amino acid levels. In the absence of a more direct assessment of the degree of insulin deficiency those ketotic patients are considered to be "relatively insulin deficient".

Although the patients and their controls were subjected to comparable workloads, the increase in blood lactate levels was significantly higher in the diabetics when compared with the control group. An identical observation has been made by Wahren et al [58] measuring blood lactate levels as well as lactate production of contracting muscles in patients with diabetes mellitus. Similarly, an increase in lactate production, an inhibition of lactate oxidation, and a decrease of (active) pyruvate dehydrogenase activity, was demonstrated when an isolated skeletal muscle preparation of streptozotocin – diabetic rats was perfused [9, 29, 30]. The reason for this metabolic difference between contracting muscles in normal and diabetic organisms is at present unknown. But it is noteworthy that the course of blood lactate concentrations during the exercise test in the two groups of diabetic patients was virtually identical, despite substantial differences in blood levels of ketone bodies and FFA.

During short-term intensive exercise in normals as well as in diabetics, an increase in the release of alanine from the contracting muscles and a rise in blood alanine levels have been demonstrated [24, 50, 58]. The mild work intensity employed in this study did not induce a rise of blood alanine (nor of lactate) in normal controls; in contrast, towards the end and following the exercise period, there was a significant fall of blood alanine. Accordingly, a significant increase of both splanchnic alanine uptake [1] and plasma glucagon levels [1] were observed only after prolonged periods of mild physical activity. Previously, it has been shown that gluconeogenesis is increased after two to three hours of mild endurance exercise [1, 25]; Chiasson et al. [16] in turn demonstrated that physiological amounts of glucagon stimulate gluconeogenesis from alanine in man. Hence, it appears likely that the late fall of blood alanine in the control subjects of this study is due to a stimulation of gluconeogenesis by increased circulating levels of glucagon. On the other hand, alanine concentrations exhibited a transient rise in both groups of diabetics confirming the data of short-term exercise experiments reported by Wahren et al. [58]. Blood concentrations of branched chain amino acids were unaffected by exercise in all three experimental groups.

As expected, blood levels of FFA and ketone bodies were largely increased in the insulin deficient diabetics. The rise of serum FFA levels induced by endurance exercise was in accordance with results of similar previous studies [1, 58]. In the ketotic diabetics the increase of FFA was somewhat accelerated (Fig. 2), probably due [15, 23] to an earlier rise (Fig. 6) of growth hormone and elevated cortisol levels (Fig. 8) observed in these patients. However, the total absolute increase of FFA concentrations in response to the exercise test was almost identical in all three groups.

The pattern of blood ketone body concentration changes during exercise showed considerable differences between the two groups of diabetics. The rise of ketone bodies in controls and diabetics in "metabolic control" was moderate and statistical significance was only reached after 150 min of exercise. In contrast, ketotic diabetics exhibited an immediate sharp rise in ketone bodies which persisted even 30 min after cessation of exercise; as a consequence, during the 3½ hours of the experiment, a substantial aggravation of ketosis developed. One explanation for the rapid augmentation of ketosis during exercise in these patients is the insulin deficiency leading to both increases of serum FFA and splanchnic ketone body production rates [58]; a second cause may be the increase in plasma glucagon

closely associated in time with the sharp rise of ketone bodies. In fact, as shown in insulin deprived juvenile diabetics at rest [2, 27], a significant correlation between the mean values of plasma glucagon and blood ketone bodies was found. It seems therefore conceivable that the exercise ketosis is at least in part due to a rise of plasma glucagon since it has been demonstrated in man that glucagon increases hepatic ketogenesis [39, 53]. Furthermore, the considerable increase of serum cortisol in ketotic diabetics (Fig. 8) might indirectly contribute to the rapid aggravation of ketosis in insulin-deficient diabetics [15]. Of additional importance might be an inhibition of peripheral ketone body utilization in these patients, as suggested on the basis of animal experiments [4, 52].

During exercise, blood glucose homoeostasis is usually maintained by an appropriate increase of splanchnic glucose production in response to a rise in peripheral glucose utilisation [25]. Any change in blood glucose levels during physical activity reflects an imbalance between these processes. In accordance with the study of Pruett [48] exercise induced a progressive fall of blood glucose in the diabetic patients in "moderate control" as well as in the normal controls. For both groups, this effect of exercise was significant within one hour after the onset of exercise. In contrast, an increase of blood glucose was observed in the ketotic patients; this finding is in accordance with earlier studies on diabetic animals [44, 54, 62] and similar to a recent observation in a subgroup of four diabetic patients during more intensive short-term exercise [58].

The apparent interactions between the actual degree of control and the effect of muscular exercise on blood glucose in juvenile type diabetics are more precisely described by significant correlations between various initial metabolic variables and the percent change in glycaemia induced by the exercise test (Fig. 5, Table 3). All these metabolic variables, i. e. blood concentrations of glucose, free fatty acids, ketone bodies and branched chain amino acids after an overnight fast, are known to be sensitive indicators of insulin availability or deficiency. At an excessive degree of insulin deficiency, blood glucose rises in response to exercise, presumably due to an imbalance of splanchnic glucose production and peripheral glucose utilization.

On the basis of animal experiments Berger et al [10] have demonstrated that insulin exerts a permissive effect with respect to the stimulation of muscle glucose uptake by contractions. Hence we suggest that the potentially blood glucose lowering effect of physical exercise in diabetics – similar to the stimulation of muscle glucose uptake by contraction – is dependent upon the presence of small amounts of insulin, and that in insulin deficiency the exercise induced increase in splanchnic glucose production cannot be balanced by an appropriate increase in peripheral glucose uptake. Recent data on pancreatectomized dogs [57] and on glucose uptake of contracting muscle in insulin deprived juvenile diabetics [55], strongly support this hypothesis. Whether the substantial elevations of FFA and ketone bodies might additionally contribute to an inhibition of peripheral glucose uptake in ketotic diabetics, as suggested by studies using the isolated perfused heart [49], cannot be ruled out since peripheral glucose uptake was not measured; however, a recent study on isolated rat skeletal muscle during exercise does not support this possibility [9]. In addition, the exaggerated increases of hormone levels, such as glucagon (Fig. 7), cortisol (Fig. 8) and possibly catecholamines [17] might contribute to the exercise induced rise in blood glucose in ketotic diabetics, because all these hormones have been reported to increase hepatic glucose output [14, 21, 22, 26, 31]. However, since no data on hepatic glucose production were obtained in this study and Wahren et al. [58] did not report increased splanchnic glucose output in ketotic versus non-ketotic diabetics during short-term exercise, these hypotheses remain speculative.

The results of this study substantiate the clinical experience that, in contrast to the possibly beneficial effects of exercise in moderately well controlled juvenile type diabetes, in ketotic, relatively insulin deficient patients, even non-strenuous exercise can induce severely disadvantageous consequences.

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