CHANGES IN FAT AND CARBOHYDRATE METABOLISM CAUSED BY MODERATE EXERCISE IN PATIENTS WITH ACROMEGALY

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SUMMARY

1. Seven patients with acromegaly and nine controls were studied before, during and after 30 min of moderate steady exercise on a bicycle ergometer. Venous blood samples were taken for estimation of growth hormone (HGH), immunoreactive insulin (IRI), pyruvate, lactate, glucose, free fatty acids (FFA), glycerol and ketone bodies.

2. Exercise caused a rise in HGH concentrations in the acromegalic patients, despite their pituitary tumour, and also in control subjects. Concentrations of IRI fell during exercise in control subjects, but rose in the acromegalic patients.

3. Concentrations of glycerol, FFA and ketone bodies rose rapidly to a maximum during exercise in the acromegals and appeared to be suppressed before the end of exercise: there was no increase in the concentration of ketone bodies after exercise. In control subjects there was a gradual increase in glycerol and FFA concentrations towards the end of exercise, but no change in ketone bodies occurred until the post-exercise period, when ketone-body concentrations rose.

4. We conclude that exercise causes remarkable differences in metabolite concentrations in the blood of acromegalic patients compared with controls, with the concentration of fat metabolites reaching a maximum, then decreasing during the period of constant exercise. There was also elevation, instead of the normal fall, of plasma IRI activity and it is suggested that the decreased concentration of fat metabolites occurred because of the change of insulin concentration. It is further suggested that in acromegaly insulin retains its effect on re-esterification of fat in spite of resistance to its effects on carbohydrate metabolism.

Key words: acromegaly, fat metabolism, carbohydrate metabolism, exercise.

Patients with hypopituitarism, whose plasma concentration of human growth hormone (HGH) cannot increase, nevertheless show a rise in the concentrations of free fatty acids.
(FFA) and ketone bodies during and after exercise (Johnson, Rennie, Walton & Webster, 1971). These results indicate that the development of post-exercise ketosis does not depend upon the presence of HGH. HGH may be a factor, however, in the regulation of metabolism during exercise in some situations, for exercise normally causes concentrations of HGH to rise (Hunter, Fonseka & Passmore, 1965). Athletes, who have lower concentrations of ketone bodies after exercise compared with controls (Johnson, Walton, Krebs & Williamson, 1969), have a smaller increase of HGH concentrations (Sutton, Young, Lazarus, Hickie & Makarylis, 1968). An opportunity to examine further the metabolic effect of HGH during exercise is provided by the study of patients with acromegaly, who secrete an excess of HGH. We have therefore studied a group of patients with acromegaly, who exercised for 30 min to determine the way in which their metabolic responses differ from those of normal subjects and patients with hypopituitarism. We describe remarkable differences in the patterns of metabolites which are discussed in relation to the actions of HGH and insulin.

METHODS

Subjects

Seven female patients (aged 24–57 years) with acromegaly and nine controls (four male and five female, aged 25–63 years) were studied. The patients had mean heights of 166 cm (±2.4 SEM) and mean weights of 68.8 kg (±6.2 SEM). The controls had a mean height of 167 cm (±3.1 SEM) and weighed 70.2 kg (±6.8 SEM). The patients had clinical symptoms of a pituitary tumour and acromegaly. Histological studies after operation indicated a pituitary adenoma of either eosinophilic, chromophobic or mixed type. All patients were studied before operation. Two patients only were receiving drugs (0.1 mg of thyroxine daily) at the time of investigation. The control subjects were matched as far as possible for height and weight and none was known to have a metabolic disorder. Five were in hospital for treatment of conditions unrelated to acromegaly, including late-onset epilepsy, cervical spondylosis and meningioma. No subject had undergone operation before the study and they were not receiving drugs at the time of the investigation. All subjects were eating normal diets with no restrictions.

Procedure

Patients and controls were brought to the laboratory between 09.30 and 11.00 hours after overnight fasting. The investigation had been explained to all subjects and their consent obtained. The subjects were exercised for a period of 30 min on a bicycle ergometer [Elma Schölander constant load ergometer (EM 369) for most investigations] fixed at a work load of 500±100 kpm/min.

Heart rate was recorded using an electrocardiograph (lead system II) during the investigations. A catheter was placed in the antecubital vein and blood samples were taken before exercise, at 5 min intervals during exercise and then at 30, 60 and 90 min afterwards. Samples were also taken at 120 and 150 min in the investigations upon three patients. Each blood sample was divided into two parts; 5 ml was deproteinized by addition to 10% perchloric acid. The remainder was heparinized and the plasma separated by centrifugation. All specimens were then stored on ice. The deproteinized samples were analysed for lactate and pyruvate (Hohorst, Kreutz & Bücher, 1959), acetoacetate and 3-hydroxybutyrate (Williamson, Mellanby & Krebs,
Metabolic effects of exercise in acromegaly

1962), glucose (Bergmeyer & Bernt, 1963) and glycerol (Kreutz, 1962). The plasma sample was analysed for FFA (Itaya & Ui, 1965) and HGH by a radio-immunoelectrophoretic method (Hunter & Greenwood, 1962) using MRC Standard A. Plasma levels of insulin (IRI) were measured by a charcoal immunoassay (Hunter, 1969; Hunter & Ganguli, 1971) in four patients and five controls. Significance of difference was tested using the Mann-Whitney U non-parametric test for small samples.

Heart rates during exercise

The resting heart rates were 90 (±5 SEM) beats/min in the patients and 82 (±4 SEM) beats/min in the controls. In both groups heart rate increased rapidly during the first 5 min of exercise (controls 79%, patients 78%) after which the rate was steady until the end of exercise when a rapid fall occurred to within 10–20% of the resting heart rate 15 min after exercise. The percentage heart-rate changes in the patients and the controls were not significantly different at any time during exercise or the post-exercise period.

Metabolites

Glucose. At rest, the blood glucose concentration was 81 mg/100 ml (±7 SEM) in the patients and 75 mg/100 ml (±4 SEM) in the controls. At the end of exercise the values were
84 mg/100 ml (±8 SEM) in the patients and 79 mg/100 ml (±6 SEM) in the controls. There was little change in the values in either group during the remainder of the study.

**Pyruvate** (Fig. 1). Resting blood pyruvate concentrations were similar in both groups. Exercise caused a rapid rise in pyruvate concentrations to a peak at 15 min which was slightly greater in the patients, but the difference was not significant \((P>0.05)\). Pyruvate concentrations fell during the second half of the exercise period in each group, but in the acromegalics they were still significantly above the resting value 60 min after the end of exercise. In the control subjects pyruvate concentrations had almost fallen to resting values 30 min after exercise. The results in the two groups were significantly different at the end of exercise and at 30 \((P<0.05)\) and 60 \((P<0.05)\) min after exercise; after 90 min, however, there was no significant difference \((P>0.05)\).

**Lactate** (Fig. 1). Resting concentrations of lactate were similar in both groups. Rapid elevation of blood lactate values to a peak at 15 min of exercise occurred in both groups, the maximum being significantly greater in the acromegalics. The concentrations in the acromegalics remained significantly different \((P<0.05)\) from their resting values for the succeeding
15 min of exercise and for 60 min after exercise. The controls, however, showed a more rapid return to approximately pre-exercise values so that there was no significant difference ($P > 0.05$) between the resting value and the value 30 min after the end of exercise.

**Glycerol** (Fig. 2). Resting glycerol concentrations were not significantly different between the groups. Blood glycerol concentrations increased during exercise earlier in the patients. The

![Graph showing plasma HGH and plasma IRI concentrations](image-url)

**Fig. 3.** Plasma HGH (µunits/ml, means ± 1 SEM) in nine control subjects (●) and seven acromegalic patients (■) and plasma IRI (µunits/ml, means ± 1 SEM) in five control subjects (●) and four acromegalic patients (■) during and after 30 min of exercise, indicated by the hatched bar.

peak values were not significantly different, but since they occurred at different times, there was a significant difference in the 20 and 30 min concentrations of the two groups (20 min, $P < 0.01$; 30 min, $P < 0.05$).

**FFA** (Fig. 2). Resting plasma FFA concentrations were not significantly different between the two groups although they fell slightly in the early part of exercise and rose as the exercise continued. The maximum concentration occurred at 15 min in the patients and values decreased during the remainder of the exercise. The control group showed a much smaller maximum value at the end of exercise and the concentrations returned to pre-exercise values.
90 min after the end of exercise. The differences in concentrations of FFA between the two groups were significant at 15, 20 and 25 min of exercise \((P<0.05)\) and their maximum values were highly significantly different \((P<0.01)\).

**Ketone bodies** (Fig. 2). Resting concentrations of ketone bodies (acetoacetate plus 3-hydroxybutyrate) were similar in both groups, but changes during exercise were very different. After a decrease in the first 10 min the values in the patients rose rapidly to a peak 25 min after the beginning of exercise and then fell in the last 5 min of exercise. In the control group ketone-body concentrations changed little during the period of exercise but in the 90 min following exercise rose to nearly 300% of the control resting value. There was no difference in the response of the male and female controls. The concentrations of ketone bodies in the two groups were significantly different at 15, 20, 25, 30 and 120 min \((P<0.05)\).

**Plasma HGH** (Fig. 3). The acromegalic patients had characteristically high resting concentrations of HGH and the control group had low resting values. In both groups exercise caused rises in HGH concentrations to a maximum at 30 min of exercise. In the acromegals the changes in absolute values were considerable (up to 200 μunits/ml increase) and were much less in the normal subjects. In patients and controls HGH concentrations fell in the period following exercise to approximately pre-exercise values at 90 min after the end of exercise.

**Plasma IRI** (Fig. 3). Resting concentrations of IRI were significantly higher in the acromegalic patients than in the controls \((P<0.05)\). The concentration fell during exercise in the control subjects, but rose in the acromegalic patients so that the difference between the two groups at the end of exercise was considerable, the concentrations in the acromegalic patients being more than double those in the controls. In both groups IRI concentrations returned to resting values by 60 min after exercise.

**DISCUSSION**

The diagnosis of acromegaly was confirmed in the patients by the abnormally high concentrations of HGH at rest. Exercise caused a marked further rise of the HGH concentration in the patients with acromegaly, suggesting that their HGH secretory centres were able to respond to the changes associated with exercise. The percentage change in heart rate with exercise in both groups of subjects was similar, suggesting that the work done was the same.

During the first 10 min of exercise concentrations of plasma FFA and ketone bodies fell in both groups. This has been ascribed to an inhibitory effect of lactate on mobilization of fat from adipose tissue and also to a direct anticalcatabolic effect of lactate on the liver (Issekutz & Miller, 1962; Houghton, Hawkins, Williamson & Krebs, 1971). However, in a previous study of exercise in patients with hypopituitarism, no decrease of FFA concentrations occurred despite the increase of lactate concentration to values above those of controls (Johnson et al., 1971). The initial changes in concentrations of FFA and ketone bodies have also been ascribed to increased peripheral utilization (Drury, Wick & Mackay, 1941; Havel, Naimark & Borchgrevink, 1963) and this could be related in the acromegals to a greater peripheral muscle blood flow which has been demonstrated at rest in such patients (Butterfield, Garratt & Whicheelow, 1963).

After 10 min there were marked differences between the two groups in metabolite concentrations in the blood. The acromegalic patients had a substantially greater degree of fat mobilization than the controls. This resulted in the blood ketone-body concentrations reaching a maxi-
Metabolic effects of exercise in acromegaly

mum during exercise, a phenomenon we have not observed in any other subjects. The greater increase in fat metabolism in the acromegalic patients might be explained by their high concentrations of HGH, a known lipolytic agent, but its absence does not prevent lipid mobilization during exercise (Troyer, Friedberg, Horton & Bogdonoff, 1966; Johnson et al., 1971). It may nevertheless be important in facilitating the mobilization of depot fat (Hunter et al., 1965; Greenwood & London, 1966). It is unlikely to be related to marked differences in cortisol concentrations, although we have not examined this possibility.

After 20–25 min the high concentrations of glycerol, plasma FFA and ketone bodies in the acromegalic decreased. There was also no increase in ketone-body concentrations after exercise, as in the control group (Courtice & Douglas, 1936). One explanation for this might be the suggestion that HGH has a dual action on fat metabolism (Winkler, Steele & Altszuler, 1968; Johnson et al., 1971). Initially high concentrations of HGH might exaggerate fat mobilization during exercise as observed in the present study and at a later stage it might cause inhibition by accelerating the re-esterification of FFA in adipose tissue. The dual action could be mediated by two polypeptide subunits which may act antagonistically on fat and carbohydrate breakdown and synthesis (Bornstein, Krahl, Marshall, Gould & Armstrong, 1968). An alternative explanation depends upon the marked differences we have observed in IRI concentration, which decreased in the controls, as shown by other workers (Cochran, Marbach, Poucher, Steinberg & Gwinup, 1966), and rose in the acromegalic patients. The increased concentration in the acromegalic might be a response to the rapid increases in FFA and ketone bodies which are known to cause insulin release (Madison, Mebane, Unger & Lochner, 1964). A major effect of insulin is to facilitate esterification of FFA to fat (Bieberdorf, Chernick & Scow, 1970) and it is, therefore, probable that the marked decrease of glycerol, FFA and ketone-body concentrations in the acromegalic after exercise is related to their much higher IRI concentrations.

The patients also had increased concentrations of lactate and pyruvate. An increased rate of fat and oxidization increases the formation of acetyl-CoA and its subsequent oxidation in the tricarboxylic acid cycle. This may block pyruvate oxidation and, therefore, cause accumulation of lactate and pyruvate. The decline in lactate and pyruvate concentrations later in the exercise period has been previously reported in other subjects and may reflect increased blood flow in the exercising muscles (Harris, Bateman, Bayley, Donald, Gloster & Whitehead, 1968; Johnson et al., 1971).

Although our present observations might be consistent with the suggestions that HGH has a delayed or post-exercise inhibitory effect on fat metabolism (Winkler et al., 1968; Johnson et al., 1971), we have also observed a marked rise in insulin concentrations in acromegalic compared with controls during exercise. This observation suggests that insulin has a major effect upon fatty acid mobilization and re-esterification during and after exercise by acromegalic. This action of insulin appeared independent of any change in blood glucose concentrations which remained substantially unaltered.

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REFERENCES


Metabolic effects of exercise in acromegaly


