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Effects of High-Dose Growth Hormone on Glucose and Glycerol Metabolism at Rest and during Exercise in Endurance-Trained Athletes

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Context: Recombinant human-GH (r-hGH), in supraphysiological doses, is self-administered by athletes in the belief that it is performance enhancing.

Objective: The objective of this study was to determine whether r-hGH alters whole-body glucose and glycerol metabolism in endurance-trained athletes at rest and during and after exercise.

Design: This was a 4-wk double-blind placebo-controlled trial.

Setting: This study was conducted at St. Thomas Hospital (London, UK).

Participants: Twelve endurance-trained male athletes were recruited and randomized to r-hGH (0.2 U/kg·d) (n = 6) or identical placebo (n = 6) for 4 wk. One (placebo group) withdrew after randomization.

Intervention: Intervention was conducted by randomization to r-hGH (0.2 U/kg·d) or identical placebo for 4 wk.

Main Outcome Measures: Whole-body rates of appearance (Ra) of glucose and glycerol (an index of lipolysis) and rate of disappearance of glucose were measured using infusions of D-[6–6-$^2H_2$]glucose and $^2H_5$-glycerol.

Results: Plasma levels of glycerol and free fatty acids and glycerol Ra at rest and during and after exercise increased during r-hGH treatment ($P < 0.05$ *vs.* placebo). Glucose Ra and glucose rate of disappearance were greater after exercise during r-hGH treatment ($P < 0.05$ *vs.* placebo). Resting energy expenditure and fat oxidation were greater under resting conditions during r-hGH treatment ($P < 0.05$ *vs.* placebo).

Conclusions: r-hGH in endurance-trained athletes increased lipolysis and fatty acid availability at rest and during and after exercise. r-hGH increased glucose production and uptake rates after exercise. The relevance of these effects for athletic performance is not known. **(*J Clin Endocrinol Metab* 91: 320–327, 2006)**

UNDER RESTING CONDITIONS, GH stimulates lipolysis and exerts a glucose counterregulatory effect in normal and GH-deficient (GHD) adults (1–10). In GHD adults, GH administration increases lipolysis, fatty acid availability, and fatty acid uptake from the circulation during exercise (11), and sustained GH administration increases maximal oxygen uptake (VO_{2max}) (12, 13). The effects on substrate metabolism during exercise of administration of supraphysiological doses of GH to normal or endurance-trained subjects are not known, and it is also not known whether doping with GH improves exercise performance. Despite this lack of evidence, anecdotal reports as well as the seizure of GH supplies by police and customs officials suggests that doping with GH is a significant problem in a number of sports including athletics, swimming, and cycling (14, 15).

Exercise is the most potent physiological stimulus to GH release (16). Because free fatty acids (FFAs) represent an important metabolic fuel during exercise of medium and long duration, it has been hypothesized that the GH response to exercise might be important in the regulation of substrate availability and use during exercise (17, 18). One recent study has demonstrated that administration of a single dose of recombinant human-GH (r-hGH) increased plasma levels of glycerol and FFA during exercise (19), but no studies have addressed the effect of sustained supraphysiological administration of r-hGH.

We hypothesized that administration of high doses of r-hGH to endurance-trained athletes would increase lipolysis and fatty acid availability and exert potentially important effects on glucose metabolism at rest and during and after exercise. Glucose kinetics and lipolysis were quantified using stable isotopic tracers of glucose and glycerol. The dose of r-hGH administered was chosen based on anecdotal reports of doses abused by athletes (15).

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Abbreviations: CV, Coefficient(s) of variation; EE, energy expenditure; FFA, free fatty acid; GHD, GH deficient; Ra, rate(s) of appearance; Rd, rate(s) of disappearance; r-hGH, recombinant human-GH; VCO_2, carbon dioxide production; VO_2, oxygen consumption; VO_{2max}, maximal oxygen uptake.

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Subjects and Methods

Study design

Data presented here are from a 4-wk double-blind placebo-controlled trial of the administration of r-hGH to endurance-trained adult males. Protein turnover data from this study have been reported previously (20). Subjects attended for four visits. After screening (visit 1), three studies were performed to assess the effects of r-hGH administration on glucose and glycerol turnover at rest and during and after exercise. After

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the baseline study (visit 2), subjects were randomized to receive either r-hGH or identical placebo at a dose of 0.067 mg/kg body weight daily. r-hGH was self-administered as a nocturnal sc injection. The placebo vials contained the same vehicle as the r-hGH. Subjects were then studied at 1 (visit 3) and 4 (visit 4) weeks after randomization to GH administration or commencement of placebo.

Subjects

Twelve male volunteers were recruited and gave informed written consent to take part in the study, which was approved by the ethics committee of West Lambeth Health Authority. One subject withdrew for personal reasons after randomization. Data from that subject were not included in the statistical analysis.

Selection criteria included male gender; age between 18 and 40 yr; high level of habitual aerobic activity, defined as at least four 30-min sessions of continuous aerobic-type exercise per week; high aerobic fitness, defined as VO_{2max} above 45 ml/kg·min; no current participation in competition at a national or international level; and no illness or medications known to impair exercise or to alter endocrine function. Subjects were asked not to change their dietary habits or training programs during the study. On entry to the study, and after 4 wk of treatment with GH or placebo, subjects underwent a full medical history, physical examination, and routine laboratory studies (full blood count, urea and electrolytes, creatinine, total protein, albumin, total bilirubin, glucose, calcium, phosphorus, hepatic enzymes, lipid profile, and urinalysis).

Clinical protocol

On each study day, subjects were fasted overnight. In the days before the experiments, they ate their habitual diet and performed their habitual physical activities. From 24 h before the experiments, they refrained from vigorous physical activity. The study was performed between 0900 and 1400 h. A cannula (Venflon, Helsinborg, Sweden) was inserted into the antecubital fossa of one arm for isotope infusion and the contralateral dorsal hand vein, which was heated, for arterialized blood sampling (21). Baseline blood samples were taken before commencement of a primed (0.9 mmol/kg) continuous infusion of $^2H_5$ glycerol (0.06 mmol/kg·min) and a primed (12 mmol/kg) continuous infusion of D-[6–6-$^2H_2$]glucose (0.13 mmol/kg·min). After a 160-min equilibration period to reach steady-state tracer enrichment, the basal steady state was sampled (−20 to 0 min). As previously described (22), the isotope infusion rate was doubled at the start of exercise to minimize changes in enrichment, which reduce the accuracy of calculating nonsteady-state kinetics.

Exercise testing

Exercise testing was performed using an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, Holland) and Medical Graphics CPX-D Cardiopulmonary Exercise Testing System (Medical Graphics, Birmingham, UK). Expired gas was sampled continuously at the mouth. The concentration of dried gas was measured with analyzers accurate to ±1% [zirconia oxide O^2 analyzer (response time of <80 msec) and infrared CO_2 analyzer (response time of <130 msec)]. Gas volume was measured with a bidirectional differential pressure preVent Pneumotach (Medical Graphics Corp., St. Paul, MN; accuracy, ±3%).

Screening exercise test

For screening purposes, VO_{2max} was assessed. Subjects cycled to exhaustion with a starting workload of 1.5 W/kg body weight, using a smooth ramp of 25 W/min, at a cycling cadence of 80 rpm with feet strapped to the pedals. Workload at VO_{2max} was used to calculate the submaximal protocol for the main studies. The workload at which the oxygen uptake first reached a plateau was regarded as the workload at VO_{2max}.

Submaximal exercise protocol

All subsequent submaximal exercise tests used an identical protocol, consisting of three consecutive stages: stage 1 was 5 min at 1 W/kg, stage 2 was 5 min at 2 W/kg, and stage 3 was 20 min at 65% of VO_{2max}.

Indirect calorimetry

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured with use of a Medical Graphics CPX-D Cardiopulmonary Exercise Testing System. Expired gas was sampled continuously at the mouth. The concentration of dried gas was measured with analyzers accurate to ±1%: zirconia oxide oxygen analyzer with a response time of <80 msec and infrared carbon dioxide analyzer with response time of <130 msec. Gas volume was measured with a bidirectional differential pressure preVent Pneumotach (Medical Graphics Corp.) accuracy of ±3%.

Analytic methods

GH was measured by a double-antibody RIA with a detection limit of 0.3 mU/liter. The intraassay coefficients of variation (CVs) were 10.0, 4.0, and 5.4% at 1.7, 12.1, and 22.2 mU/liter, respectively. IGF-I was measured by double-antibody RIA after acid/ethanol extraction, using a commercially available reagent pack (Amersham, Arlington Heights, IL; within-assay CV < 5%). Serum free T_4 and free T_3 were measured by RIA (CV < 2%). Insulin was measured by double-antibody RIA (within-assay CV, 6%). FFA levels were measured with an enzymatic method using a commercially available kit (Wako Laboratories, Neuss, Germany) on a Cobas Fara autoanalyzer with an interassay CV of 3.6%.

Glucose enrichment was determined by gas chromatography-mass spectrometry (HP 5971A MSD, Agilent Technologies, Berkshire, UK) using the penta-*O*-trimethylsilyl-*O*-methyloxime derivative monitoring the ions 319 and 321 for the unlabeled and D-[6–6-$^2H_2$]glucose, respectively. Glycerol enrichment was determined by gas chromatography mass spectrometry on a HP 5971A MSD (Agilent Technologies) using a method modified from Elia *et al.* (23). Glycerol was isolated from deproteinized plasma using ion exchange chromatography and the Tris-trimethylsilyl derivative formed. Gas chromatography-mass spectrometry analysis used electron impact ionization with selected ion monitoring of the ions at m/z 205 and 208. Glycerol concentration was measured using a commercially available colorimetric assay (Randox Laboratories Ltd., Co. Antrim, UK) on an automated analyzer.

Calculations

An isotopic steady state was achieved during the last 20 min of the basal (preexercise) period, so Steele's equation for steady-state kinetics was used (24). During and after exercise, nonsteady-state conditions were present, and Steele's equation for nonsteady-state kinetics was used to determine glycerol rate of appearance (Ra), glucose Ra, and glucose rate of disappearance (Rd) (23). Volumes of distribution of glucose and glycerol were assumed to be 100 and 230 ml/kg, respectively (25).

Calculation of energy expenditure (EE) and substrate oxidation

EE and substrate oxidation were calculated from the following equations: EE = 3.91 VO_2 + 1.10 VCO_2 − 0.53 protein oxidation, fat oxidation = 1.67 VO_2 − 1.67 VCO_2 − 0.31 protein oxidation, and carbohydrate oxidation = 4.55 VCO_2 − 3.21 VO_2 − 0.46 protein oxidation (26). Protein oxidation was calculated from leucine turnover studies (20) as previously described (27). Carbohydrate, lipid, and protein oxidation are expressed as grams per minute. VO_2 represents oxygen consumption, and VCO_2 represents VCO_2 in liters per minute.

TABLE 1. Baseline characteristics of the study subjects

	r-hGH-treated	Placebo-treated
Age (yr)	31 (23–40)	33 (27–42)
Height (cm)	175 (174–183)	177 (171–180)
Weight (kg)	76 (68–81)	75 (66–82)
BMI (kg/m^2)	24 (23–26)	25 (24–26)
VO_{2max} (ml/min·kg)	54.2 (50.1–60)	53.4 (49.4–60)

Values are mean (range).

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TABLE 2. Plasma hormone levels at baseline, 1, and 4 wk in athletes who were randomized to treatment with rhGH or placebo

	r-hGH-treated			Placebo-treated		
	Baseline	1 wk	4 wk	Baseline	1 wk	4 wk
IGF-I (nmol/liter)	24.6 ± 3.0	89.6 ± 12.2	106.3 ± 16.4[a]	25.8 ± 2.7	25.4 ± 2.7	25.2 ± 2.6
Free T_3 (pmol/liter)	5.1 ± 0.3	6.0 ± 0.1	6.1 ± 0.2[a]	4.8 ± 0.2	4.9 ± 0.2	4.8 ± 0.1
Free T_4 (pmol/liter)	15.5 ± 1.5	11.5 ± 1.0	10.6 ± 0.9[a]	15.8 ± 1.6	15.6 ± 1.7	15.8 ± 1.5

Data represent means ± SEM.
[a] $P < 0.05$ *vs.* placebo.

Statistical analyses

Results are expressed as mean ± SE. Analysis was carried out on the composite end-points of mean resting levels, mean levels during exercise, and area under the curve postexercise. To determine the effects of r-hGH on each end-point, repeated measures ANOVA was carried out with treatment (GH or placebo) as a grouping factor.

Results

We studied 11 males, six subjects being randomized to the r-hGH-treated group and five to the placebo-treated group. Mean age, height, weight, and VO_{2max} did not differ between the two groups (Table 1). Baseline IGF-I was within the normal laboratory reference range for both groups (Table 2). Compliance assessed by counting used vials was 100%. Physical examination and routine laboratory measures remained unchanged in subjects who received r-hGH, and those who received placebo. There were few side effects reported by those who had received r-hGH treatment; one individual noted ankle swelling and transient arthralgia, which resolved within 48 h of commencing treatment, and another reported general fatigue and reduced concentration.

Plasma hormone levels (Fig. 1)

In the baseline studies, plasma levels of GH increased during exercise ($P < 0.005$ *vs.* resting) and decreased to resting values 60 min after exercise. Plasma levels of insulin did not change significantly during exercise. During r-hGH administration, resting plasma levels of GH increased ($P < 0.05$ *vs.* placebo). During exercise, plasma GH levels did not change, and levels were decreased compared with the placebo group ($P < 0.05$ *vs.* placebo). During r-hGH administration, plasma insulin levels were greater than in the placebo group at rest and during and after exercise ($P < 0.05$ *vs.* placebo). As previously reported (20), during r-hGH administration, IGF-I levels rose markedly, reaching levels outside the physiological range ($P < 0.05$ *vs.* placebo, Table 2). r-hGH also increased free T_3 into the supraphysiological range and reduced free T_4 ($P < 0.05$ *vs.* placebo, Table 2).

Glucose kinetics (Fig. 2)

There was no change in plasma glucose in either group between 80 min before exercise and the beginning of exercise. An isotopic steady-state was achieved in both groups during the 20 min before exercise. In the baseline studies, plasma levels of glucose, glucose Ra, and glucose Rd increased during exercise ($P < 0.005$ *vs.* resting) and decreased to resting values after exercise. Under resting conditions and during exercise, there was no effect of r-hGH on plasma glucose levels, glucose Ra, or glucose Rd. After exercise, glucose Ra and glucose Rd were greater during GH treatment ($P < 0.05$ *vs.* placebo) Glucose metabolic clearance rate increased during exercise and returned to baseline values after exercise but was not influenced by r-hGH administration (data not shown).

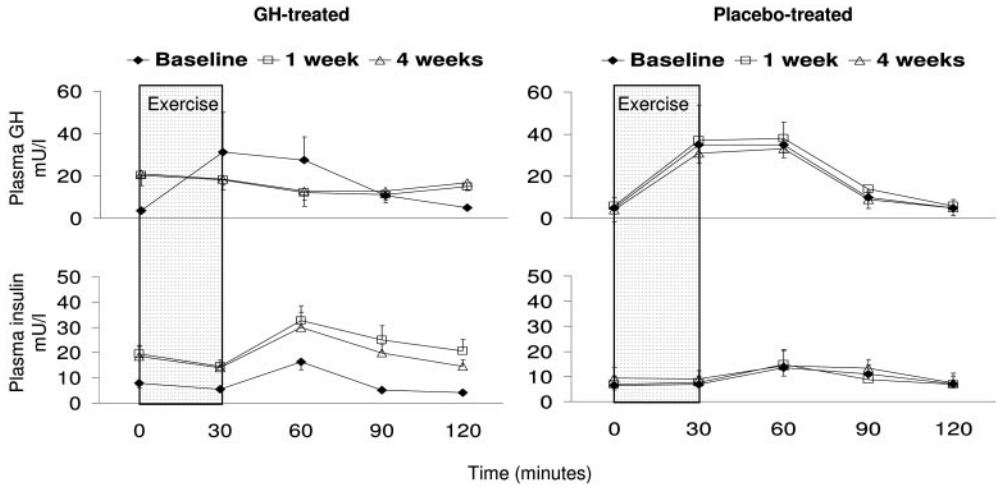

FIG. 1. Plasma levels of GH and insulin under resting conditions (0 min) and during (30 min) and after (60–120 min) exercise at baseline and 1 and 4 wk in athletes who were randomized to treatment with r-hGH (*left panel*) or placebo (*right panel*). Plasma GH was increased ($P < 0.05$) by r-hGH (*vs.* placebo) at rest and after exercise and decreased ($P < 0.05$) by r-hGH (*vs.* placebo) during exercise. Plasma insulin was increased ($P < 0.05$) by r-hGH (*vs.* placebo) at rest and during and after exercise.

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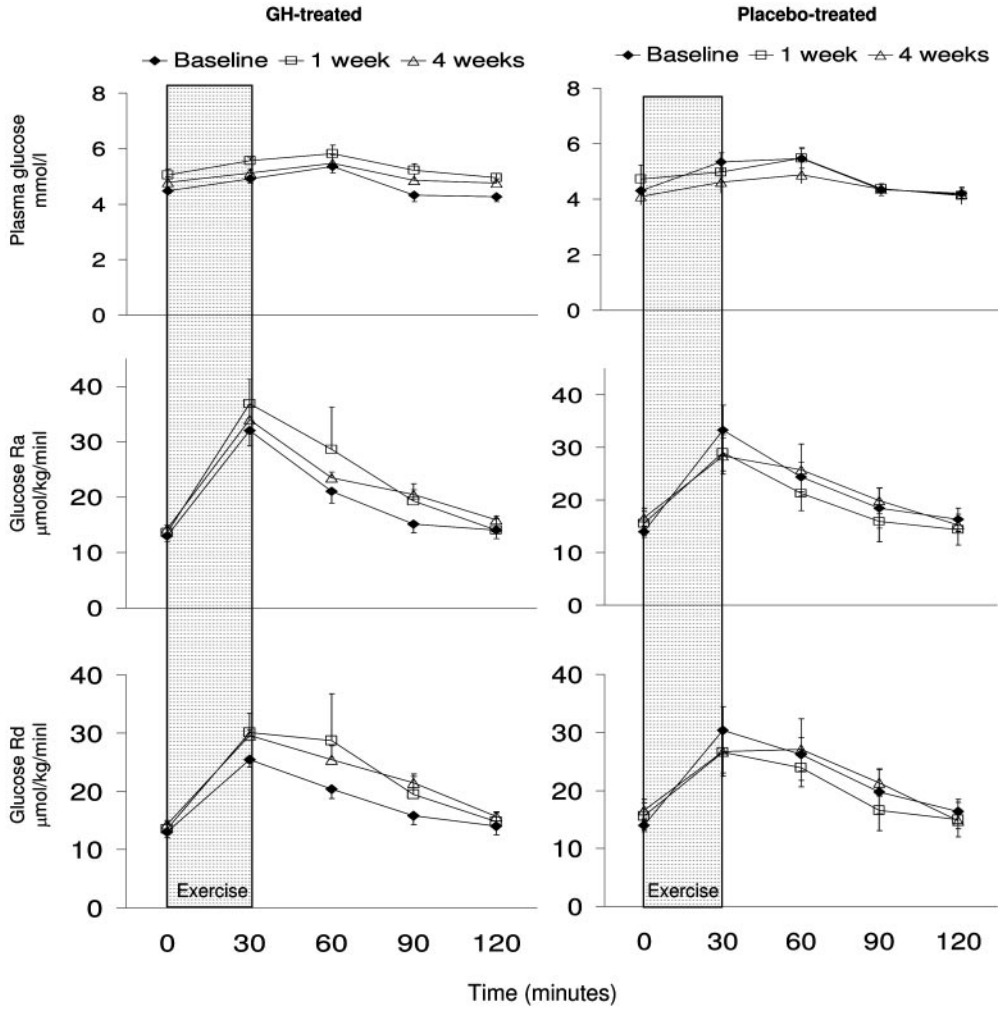

FIG. 2. Plasma levels and Ra and Rd of glucose under resting conditions (0 min) and during (30 min) and after (60–120 min) exercise at baseline and 1 and 4 wk in athletes who were randomized to treatment with rhGH (*left panel*) or placebo (*right panel*). Glucose Ra and glucose Rd were increased ($P < 0.05$) by r-hGH (*vs.* placebo) after exercise.

Glycerol kinetics (Fig. 3)

There was no change in plasma glycerol in either group between 80 min before exercise and the beginning of exercise. An isotopic steady state was achieved in both groups during the 20 min before exercise. In the baseline studies, plasma levels of glycerol and glycerol Ra increased during exercise ($P < 0.005$ *vs.* resting) and decreased to resting values after exercise. Plasma levels of FFA did not change significantly during or after exercise. During r-hGH treatment, a similar pattern was seen with plasma levels of glycerol and glycerol Ra increasing during exercise and decreasing to resting values after exercise. Plasma glycerol, glycerol Ra, and plasma FFA were greater during GH treatment at rest and during and after exercise ($P < 0.05$ *vs.* placebo). There were no differences between the effect of 1 and 4 wk of r-hGH treatment.

Resting EE and substrate oxidation (Table 3)

In the baseline studies, EE, fat oxidation, and carbohydrate oxidation increased during exercise ($P < 0.005$) *vs.* resting and decreased to resting values after exercise. During r-hGH treatment, a similar pattern was seen with EE, fat oxidation, and carbohydrate oxidation all increasing during exercise and decreasing to resting values after exercise. During r-hGH treatment, EE and fat oxidation increased ($P < 0.05$ *vs.* placebo) under resting conditions. During and after exercise, there were no differences observed compared with the baseline studies.

Discussion

This double-blind placebo-controlled study demonstrates that administration of supraphysiological doses of r-hGH to endurance-trained athletes influences substrate metabolism under resting conditions and during exercise. r-hGH increased lipolysis and plasma levels of glycerol and FFA at rest and during and after submaximal exercise. r-hGH did not influence glucose turnover at rest or during exercise but increased rates of glucose production and glucose uptake after exercise. During treatment with r-hGH, plasma levels of GH were increased under resting conditions but did not increase in response to exercise, whereas plasma levels of

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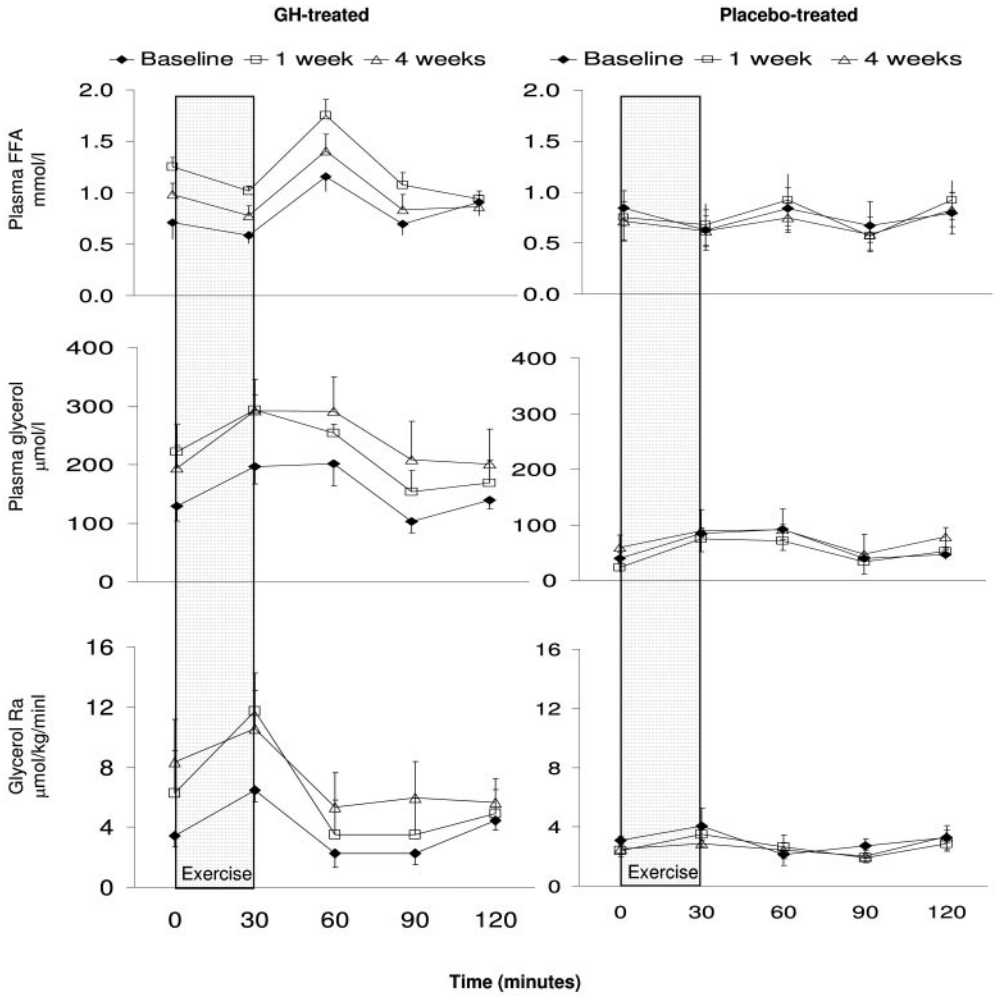

FIG. 3. Plasma levels of glycerol and FFAs, and glycerol Ra under resting conditions (0 min) and during (30 min) and after (60–120 min) exercise at baseline and 1 and 4 wk in athletes who were randomized to treatment with rhGH (*left panel*) or placebo (*right panel*). All measurements were increased ($P < 0.05$) by r-hGH (*vs.* placebo) at rest and during and after exercise.

insulin were increased under resting conditions and during exercise.

We have demonstrated recently in GHD adults that rates of lipolysis and FFA turnover, at rest and during exercise, are greater during GH replacement (11). The current study extends these findings by demonstrating that in healthy GH-replete subjects both under resting conditions and during exercise, lipolysis and FFA availability are enhanced by administration of supraphysiological doses of r-hGH. *In vitro* studies and studies in animal models have shown that the effect of GH to increase lipolysis is both direct and by enhancing the effect of adipocytes to respond to lipolytic factors such as catecholamines (28–30). Most previous studies that have investigated the effects of supraphysiological r-hGH administration under conditions of exercise were undertaken with a view to developing a test to detect GH abuse and concentrated on changes in components of the GH-IGF-I system and markers of bone and connective tissue turnover (31, 32). r-hGH was shown to increase IGF-I and IGF binding proteins and to reduce the GH response to exercise (31). To our knowledge, only one previous study has investigated the effects of supraphysiological GH administration on intermediate metabolism during exercise. Lange *et al.* (19) demonstrated that plasma levels of glucose, glycerol, FFA, and lactate were greater during moderate- to high-intensity exercise in trained men after administration of a single dose of r-hGH, 2.5 mg sc, 4 h before exercise. There are important differences between that study and the current one. Firstly, the current study demonstrates the effects of prolonged rather than acute GH administration. Secondly, the timing of GH administration in the study of Lange *et al.* (19) resulted in increased GH levels during exercise in contrast to the current study in which GH levels were lower during exercise. Finally, the current studies were carried out in the postabsorptive setting, whereas the study of Lange *et al.* (19) was carried out postprandially. Taken together, the findings of these two studies suggest that GH enhances lipolysis during exercise under both postabsorptive and postprandial conditions and that the lipolytic effect of GH during and after exercise does not depend on increased circulating levels of GH during exercise.

The effect of GH to increase fat oxidation at rest is well established in both GHD and normal subjects (6, 27, 33, 34), whereas the observation that r-hGH administration did not

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TABLE 3. Energy expenditure, carbohydrate (CHO) oxidation, and fat oxidation at baseline, 1, and 4 wk in athletes who were randomized to treatment with r-hGH or placebo

	r-hGH-treated (min)					Placebo-treated (min)				
	0	30	60	90	120	0	30	60	90	120
Energy expenditure (kcal/min·kg)										
Baseline	0.02 ± 0.00	0.16 ± 0.01	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.17 ± 0.01	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00
1 wk	0.02 ± 0.00	0.17 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.17 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00
4 wk	0.02 ± 0.00	0.17 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.17 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00
Respiratory quotient										
Baseline	0.79 ± 0.02	0.91 ± 0.01	0.79 ± 0.02	0.78 ± 0.01	0.82 ± 0.03	0.82 ± 0.02	0.91 ± 0.01	0.76 ± 0.02	0.77 ± 0.01	0.81 ± 0.02
1 wk	0.78 ± 0.01	0.89 ± 0.01	0.83 ± 0.03	0.77 ± 0.01	0.79 ± 0.01	0.82 ± 0.02	0.91 ± 0.01	0.80 ± 0.03	0.77 ± 0.02	0.77 ± 0.03
4 wk	0.78 ± 0.01	0.90 ± 0.01	0.79 ± 0.01	0.81 ± 0.04	0.76 ± 0.02	0.80 ± 0.01	0.90 ± 0.01	0.81 ± 0.01	0.79 ± 0.02	0.75 ± 0.01
CHO oxidation (mg/min·kg)										
Baseline	1.0 ± 0.5	28.0 ± 1.1	1.0 ± 0.2	0.9 ± 0.2	1.3 ± 0.4	1.6 ± 0.3	31.3 ± 1.8	0.7 ± 0.2	0.7 ± 0.2	1.3 ± 0.3
1 wk	1.1 ± 0.2	30.1 ± 0.7	1.9 ± 0.2	1.1 ± 0.3	1.4 ± 0.2	1.6 ± 0.4	32.1 ± 1.1	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.6
4 wk	1.2 ± 0.3	30.5 ± 0.9	1.2 ± 0.3	1.5 ± 0.8	0.7 ± 0.4	1.4 ± 0.2	31.1 ± 2.4	1.1 ± 0.3	1.1 ± 0.3	0.5 ± 0.2
Fat oxidation (mg/min·kg)										
Baseline	1.0 ± 0.1	5.1 ± 0.3	1.0 ± 0.2	1.1 ± 0.2	0.9 ± 0.3	0.9 ± 0.1	5.1 ± 0.8	1.3 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
1 wk	1.4 ± 0.1	5.6 ± 0.2	1.1 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.0 ± 0.1	5.0 ± 0.6	1.3 ± 0.3	1.4 ± 0.2	1.6 ± 0.3
4 wk	1.3 ± 0.1[a]	5.4 ± 0.3	1.3 ± 0.2	1.0 ± 0.2	1.4 ± 0.2	1.1 ± 0.1	5.6 ± 0.6	1.0 ± 0.1	1.2 ± 0.1	1.4 ± 0.1

Data represent means ± SEM.
[a] $P < 0.05$ *vs.* placebo.

influence fat oxidation during exercise is novel. The more marked effect of GH under resting conditions might reflect maximally or near-maximally stimulated fat oxidation during exercise of this intensity even before r-hGH administration. Alternatively, there is *in vitro* evidence that GH increases fat oxidation through a direct effect on mitochondria (35); therefore, any effect of GH to stimulate fat oxidation during exercise would be dependent on increased circulating GH levels during exercise, which did not occur in the current study.

The effect of GH on glucose metabolism is complex and differs between GHD and GH-replete subjects and after acute, short-term, and long-term administration. The acute insulin-like effect of GH that occurs within minutes of administration is probably not physiologically relevant in humans (36, 37). The later antiinsulin or counterregulatory effect of GH is characterized by increased hepatic glucose production, reduced glucose uptake into skeletal muscle, and increased insulin secretion (2–7, 10). There is increasing evidence that this effect may occur secondary to the lipolytic effect of GH (38). Long-term GH replacement in GHD adults does not worsen insulin sensitivity compared with baseline (39–46), probably reflecting a balance between the insulin antagonistic effect of GH and the insulin-sensitizing effects of increased lean body mass and reduced body fat, but sustained exposure to supraphysiological r-hGH in the pathophysiological model of acromegaly causes insulin resistance, glucose intolerance, and frank diabetes (47–50). In the current study, r-hGH increased the Ra into and disappearance from the circulation of glucose after exercise but did not alter glucose kinetics under resting conditions. The lack of effect of GH on resting rates of glucose turnover has been reported previously (2–5, 37, 51) and may be due to a compensatory increase in plasma insulin (35), which was also observed in the current study. The observation that glucose turnover after exercise was increased by GH administration is novel and provides further evidence of a metabolic interaction between GH and exercise.

This study did not address the question of whether supraphysiological GH enhances exercise performance in GH-replete subjects. Exercise capacity is reduced in GHD subjects and improved after GH replacement (12, 13, 52). Fat is an important fuel during mild to moderate exercise, and increased fatty acid availability could theoretically prolong exercise by sparing limited carbohydrate stores (53, 54). However, despite an increase in lipolysis and fatty acid availability, there was no effect of GH on fat oxidation during exercise in either the current study or that reported by Lange *et al.* (19). These observations can be explained by studies that have reported that increased availability of FFA during low to moderate intensity does not lead to a further increase in fat oxidation (55, 56). Additional evidence that the observed metabolic effects of supraphysiological GH are not reflected in improved athletic performance comes from three recent studies. Berggren *et al.* (57) administered supraphysiological GH for 28 d to healthy active normal subjects and found no change in VO_{2max} or maximal power output during cycling. In the study reported by Lange *et al.* (19), GH administration led to a significant increase in plasma lactate during 90 min of cycling at 65 and 75% of VO_{2max} during GH administration that was associated with reduced exercise performance in some subjects. Hansen *et al.* (58) observed no effect of GH administration on fat oxidation in well-trained subjects during 120 min of cycling at 55% of VO_{2max}, despite a marked increase in lipolysis. Although these observations argue against a beneficial effect of supraphysiological GH during exercise, we cannot rule out a potentially advantageous effect of GH administration in the posttraining setting. For example, increased fatty acid concentrations postexercise could be advantageous in replenishing muscle triglyceride stores.

Several limitations of the study should be addressed. The study population was relatively small; consequently, it is possible that some metabolic effects of GH were not identified. We did not address whether the observed effects reflected administration of GH over the previous 7 or 28 d or whether similar effects would have been seen after a single GH injection the night before the studies. Finally, we did not address which, if any, effects were direct effects of GH and

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which reflected complex interactions between glucose and fatty acids and with other hormones including insulin, thyroid hormones, and catecholamines.

In summary, administration of supraphysiological GH to endurance-trained athletes results in potentially important effects on substrate metabolism. Lipolysis and fatty acid availability were increased under resting conditions and during and after exercise, whereas glucose turnover was increased after exercise. Further studies are needed to demonstrate whether these metabolic findings are relevant to clinical situations.

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