

# Effect of exogenous growth hormone and exercise on lean mass and muscle function in children with burns

Oscar E. Suman,<sup>1,2</sup> Steve J. Thomas,<sup>1</sup> Judy P. Wilkins,<sup>1</sup>  
Ronald P. Mlcak,<sup>1</sup> and David N. Herndon<sup>1,2</sup>

<sup>1</sup>Shriners Hospitals for Children, Galveston 77550; and <sup>2</sup>Department of Surgery,  
The University of Texas Medical Branch, Galveston, Texas 77555

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**Suman, Oscar E., Steve J. Thomas, Judy P. Wilkins, Ronald P. Mlcak, and David N. Herndon.** Effect of exogenous growth hormone and exercise on lean mass and muscle function in children with burns. *J Appl Physiol* 94: 2273–2281, 2003. tk;1 First published February 14, 2003; 10.1152/jappphysiol.00849.2002.—We tested the hypothesis that the administration of recombinant human growth hormone (rHGH) and exercise would increase lean body mass (LBM) and muscle strength in burned children to a greater extent than rHGH or exercise separately. Children, ages 7–17 yr, with >40% body surface area burned, were randomized into groups. One group (GHEX,  $n = 10$ ) participated in a 12-wk in-hospital physical rehabilitation program supplemented with an exercise program and received  $0.05 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  of rHGH. A second exercising group (SALEX,  $n = 13$ ) received saline. A third group (GH,  $n = 10$ ) received a similar dose of rHGH as GHEX and participated in a 12-wk, home-based physical rehabilitation program without exercise. The fourth group (Saline,  $n = 11$ ) received saline and participated in a 12-wk, home-based physical rehabilitation program without exercise. The mean ( $\pm$ SE) percent change in lean body mass after 12 wk was not significantly different between GHEX ( $9.0 \pm 2.1\%$ ), SALEX ( $5.4 \pm 1.6\%$ ), and GH ( $5.8 \pm 1.8\%$ ) groups ( $P = 0.33$ ). However, the mean percent change in muscle strength was significantly greater in the GHEX ( $36.2 \pm 5.4\%$ ) and SALEX ( $42.6 \pm 10.0\%$ ) groups than in the GH ( $-7.4 \pm 4.7\%$ ) or Saline ( $6.7 \pm 4.4\%$ ) groups ( $P = 0.008$ ). In summary, rHGH GHEX, SALEX, and GH alone produced similar improvements in LBM. However, muscle strength was only increased via exercise.

rehabilitation; burned children; thermal injury

EXOGENOUS RECOMBINANT HUMAN growth hormone (rHGH), due to its anabolic effects, has been used in humans to treat various diseases and medical conditions, such as dwarfism, cystic fibrosis, leukemia, growth delay, chronic heart failure, and aging (6, 14, 19, 20, 32, 35, 38, 39, 44).

Exogenous rHGH has also been used in the treatment of thermal injuries. Thermal injuries in children result in a delay in growth for several years after injury (1). In addition, there is persistent and extensive loss of skeletal muscle mass that leads to physical inactivity and impaired physical function (11, 16, 36). Therefore, rHGH has been administered acutely to severely

burned children and has been demonstrated to enhance wound healing, increase growth, and attenuate muscle catabolism (1, 27, 40).

The effects of rHGH administered long term (>6 mo) in burned children have also been investigated. In a study that assessed the effects of rHGH administration alone in 12 severely burned children for 1 yr, Hart et al. (15) reported an attenuation of muscle catabolism and osteopenia. However, no assessment of muscle function was done.

Growth hormone is released by both acute and chronic exercise, with the amount and manner of release being dependent on the intensity and duration of exercise (21). Because growth hormone is released with exercise, there has been considerable interest in the use of exercise alone to increase muscle mass, strength, and body growth in individuals with growth hormone deficiency or abnormalities (22).

Exercise has long been proposed as a therapeutic mode in the rehabilitation of burned victims (17). However, only recently has there been a prospective, controlled, randomized study conducted in burned children that has substantiated the proposed benefits of exercise alone (36). In that study, our laboratory (36) reported gains in isokinetic leg strength and in lean mass in response to a 12-wk exercise program consisting of aerobic and resistive exercises.

Although a greater effect of rHGH and exercise combined, than with each intervention alone, on lean mass has not been found in populations such as the elderly or young adults (37, 42, 43), in a traumatized population, such as severely burned children, this is not known. Considering the beneficial effects that growth hormone administration or exercise training alone exerts on lean body mass (LBM) in children with burns, it is possible that the combination of exercise and rHGH would increase muscle mass and strength to a greater extent than with exercise or rHGH alone.

We, therefore, designed a study to test the hypothesis that administration of rHGH and exercise would increase lean muscle mass and muscle strength to a greater extent than rHGH or exercise alone in children with burns.

Address for reprint requests and other correspondence: O. E. Suman, Shriners Hospitals for Children, 815 Market St., Galveston, TX 77550 (E-mail: oesuman@utmb.edu).

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## METHODS

**Patients.** One hundred children, age 7–17 yr old, were initially enrolled in the study. However, at discharge, 31 patients had died, declined further participation, or no longer met criteria (see criteria below). The remaining 69 patients continued in the study, but at the 9-mo postburn time point, only 44 patients had met compliance requirements or had a complete set of data. Therefore, 44 children (37 boys, 7 girls) completed the study, which was conducted at Shriners Burns Hospital-Galveston from September 1997 to January 2002. Only patients with >40% of total body surface area burned, as assessed by the “rule of nines” method (29) during excisional surgery, in the acute phase of injury, and admitted to the emergency room at our institution were initially enrolled. Patients were excluded if they had one or more of the following: leg amputation, anoxic brain injury, psychological disorders, quadriplegia, or severe behavior or cognitive disorders. Informed consent was given by the parent or legal guardian during the first day of acute admission. After informed consent was obtained, patients were randomized, irrespective of gender, into one of four groups (Fig. 1). Two of the four groups participated in a 12-wk in-hospital physical rehabilitation program, supplemented with an individualized and supervised exercise-training program. One of these exercise groups received administration of  $0.05 \text{ mg} \cdot \text{kg body wt}^{-1} \cdot \text{day}^{-1}$  of rHGH (GHEX,  $n = 10$ ); the other received administration of  $0.05 \text{ mg} \cdot \text{kg body wt}^{-1} \cdot \text{day}^{-1}$  of saline (SALEX,  $n = 13$ ). The remaining two groups participated in a 12-wk home-based physical rehabilitation program without a supervised exercise-training program. One of the home-based (no exercise) groups received rHGH administration (GH,  $n = 10$ ). The other home based group received saline (Saline,  $n = 11$ ). The dosage of rHGH was chosen based on demonstrated efficacy during long-term treatment of children with Turner syndrome and in burned children (15, 33, 34). The time chosen to start drug or saline administration (at hospital discharge) was chosen based on the clinical need to improve wound

healing or attenuate catabolism, hypermetabolism, and growth delay.

All patients received similar standard medical care and treatment from the time of emergency admission at our institution and acute care of the burn injury until time of discharge. In addition, all groups were discharged with similar standard medical and rehabilitation care until the 6-mo postburn injury time point.

One day before discharge, patients entered the study protocol (Fig. 1). On the morning of discharge (after an overnight fast of at least 8 h), blood was drawn at ~7:00 AM to determine growth hormone, IGF-I, and IGF-binding protein-3 (IGFBP-3) levels. The hormonal studies were repeated at 6 and at 9 mo after the burn injury.

At 6 mo postburn injury, all patients returned to Shriners Hospitals for Children for baseline exercise testing and assessment of body composition. This time point of 6 mo postburn injury for initial exercise assessment and exercise training represented a period when all patients were ambulatory and able to participate in strenuous exercise evaluations and training.

After completing the exercise tests, the GHEX and SALEX groups began participating in the 12-wk in-hospital physical rehabilitation program supplemented with an individualized and supervised exercise-training program. In contrast, the GH and Saline groups began participating in the 12-wk standard home-based physical rehabilitation program without a structured and supervised exercise program. The in-hospital physical rehabilitation program consisted of 12 wk of conventional occupational therapy (OT) and physical therapy (PT) twice daily for 1 h. Patients in the GH and Saline groups did not receive an exercise prescription by an exercise physiologist at any time during the study. This study was approved by the Institutional Review Board.

**Education on drug or placebo administration.** Education of the study participants and/or parents on the administration of rHGH or placebo was started early in the acute phase of treatment to allow sufficient time for understanding of the study, competence in injection technique, the importance of daily compliance, documentation on the calendar provided, safe drug handling, and storage requirements and Sharps disposal. Research nurses met frequently with the participants before they started the injections, both individually and in group sessions to ensure competence. Each participant performed return demonstrations on the proper way to administer injections, and education was continued as needed. Growth hormone or saline administration was started on the day that the patient was discharged from the hospital. This is the time point when wounds are medically considered to be 95% healed. Compliance was determined via direct observation or by a patient/guardian questionnaire by using a Self-Reported Compliance Questionnaire and set at a minimum of 75% compliance to their daily study drug for all groups. Compliance percentage was chosen from estimates for children in medical literature in which improvement in chronic therapy is achieved with a minimal compliance of 70% (7, 31).

At each hospital clinic visit (6 and 9 mo postburn), a research nurse met with all study participants, who were asked to fill out a Self-Reported Compliance Questionnaire for the time since their last clinic visit. The questions related to any problems they encountered with the study drug, adverse reaction, supplies, and how many doses of the study drug they missed. The calendars provided for documentation were reviewed if they had been used and brought to the appointment; otherwise, the number of doses missed was an estimate of compliance by the participant. Clinical staff re-

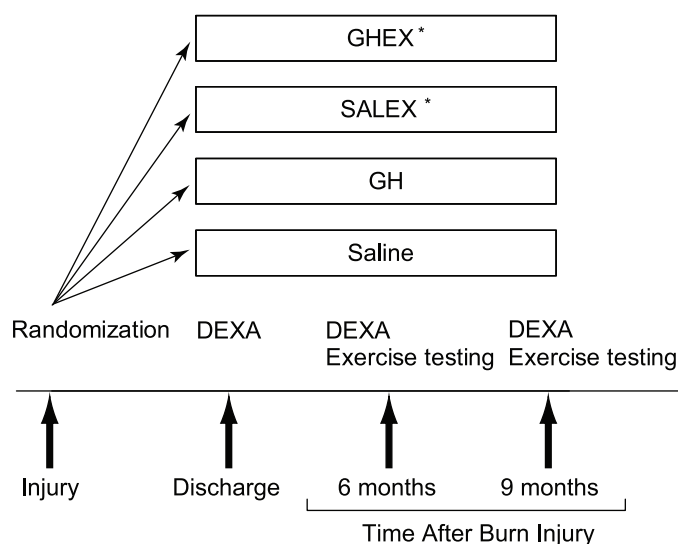


Fig. 1. Study timeline and design encompassing date of burn injury to 9 mo after burn injury. Growth hormone or saline was given, starting at discharge. Assessment of hormone levels and of body composition was done, starting at discharge. Exercise testing was done at 6 and 9 mo after burn injury. GHEX, growth hormone and exercise; SALEX, saline and exercise; GH, growth hormone alone; Saline, saline alone; DEXA, dual-energy X-ray absorptiometry. \*The 12-wk exercise program started at 6 mo postburn injury.

viewed the study, and the consent of participants for continued participation was assessed.

Data were included for 44 burned participants. All had reached the appropriate time points in their respective groups and had hormonal levels available at 6- and 9-mo time points, as well as body composition and muscle strength measurements.

**Hormone analysis.** Five milliliters of whole blood were withdrawn from an in-dwelling central line for determination of rHGH, IGF-I, and IGFBP-3 levels. Blood samples were taken after an overnight fast of at least 8 h. All levels of hormones were measured by using enzyme-linked immunosorbent assays from Diagnostic System Laboratories (Webster, TX).

**Exercise testing.** Exercise assessments were conducted at the beginning of 6 mo and at the end of 9 mo postburn injury. Before strength testing, the patient was familiarized with the exercise equipment and instructed on proper weight lifting techniques. The patient was asked to sit quietly for ~15 min before resting measurements were recorded. After this time period, vertical height and body weight were measured. A similar procedure of exercise testing was done for the non-burned children.

**Strength measurements.** Strength testing was conducted on day 1 of the 6- and 9-mo postburn injury period by using a Biodex System-3 dynamometer (Shirley, NY). The isokinetic test was performed on the dominant leg extensors and tested at an angular velocity of 150°/s. This speed was chosen as it was well tolerated (compared with lower or higher angular speeds) by the children across all ages and all groups. The patients were seated and their position stabilized with a restraining strap over the midthigh, pelvis, and trunk in accordance with the Biodex System-3 Operator's Manual. All patients were familiarized with the Biodex test in a similar manner. First, the administrator of the test demonstrated the procedure; second, the test procedure was explained to patients; and third, patients were allowed to practice the actual movement during three submaximal repetitions without load as warm-up. More repetitions were not allowed to prevent the onset of fatigue. The anatomic axis of the knee joint was aligned with the mechanical axis of the dynamometer before the test. After the three submaximal warm-up repetitions, 10 maximal voluntary muscle contractions (full extension and flexion) were performed. The maximal repetitions were performed consecutively without rest in between. Three minutes of rest were given to minimize the effects of fatigue, and the test was repeated.

Values of peak torque were calculated by the Biodex software system. The highest peak torque measurement between the two trials was selected. Peak torque was corrected for gravitational moments of the lower leg and the lever arm.

A similar procedure was carried out for assessing the muscle strength in nonburned children.

**Three-repetitions maximum test.** After a 30-min rest period, patients enrolled in the GHEX or SALEX groups were tested to determine the amount of weight or load that would be used during the first week (of the 12-wk program) as baseline loads. They were tested in the following order of exercises: bench press, leg press, shoulder press, leg extension, biceps curl, leg curl, and triceps curl. The three-repetitions maximum (3-RM) load was determined as follows. After an instruction period on correct weight lifting technique, the patient warmed up with lever arm and bar (or wooden dowel) and was allowed to become familiar with the movement. After this, the patient lifted a weight that allowed successful completion of four repetitions. If the fourth repetition was achieved successfully and with correct technique, a 1-min

resting period was allowed. After the resting period, a progressively increased amount of weight or load was instructed to be lifted at least four times. If the patient lifted a weight that allowed successful completion of three repetitions, with the fourth repetition not being volitionally possible, due to fatigue or inability to maintain correct technique, the test was terminated and the amount of weight lifted from the successful set was recorded as their individual 3 RM. A 3 RM was not done on the nonburned group of children or on the nonexercising groups (GH and Saline), as they did not exercise train for 12 wk.

**Peak oxygen consumption.** All subjects underwent a standardized treadmill exercise test with the use of the modified Bruce protocol (3) as part of their standard clinical outpatient evaluation. Heart rate and oxygen consumption were measured and analyzed by using methods previously described (23, 36). Briefly, breath-by-breath analysis was continuously made of inspired and expired gases, flow, and volume by using a Medgraphics Cardio<sub>2</sub> Combined O<sub>2</sub>/ECG Exercise System (St. Paul, MN). Speed and angle of elevation started at 1.7 mph and 0%, respectively. Thereafter, the speed and level of incline were increased every 3 min. Subjects were constantly encouraged to complete 3-min stages, and the test was terminated once peak volitional effort was achieved. The peak oxygen consumption ( $\dot{V}O_{2\text{ peak}}$ ) and peak heart rate were additionally used to establish the intensity at which patients in the GHEX and SALEX groups exercised during the 12 wk of training. A similar procedure was used to assess  $\dot{V}O_{2\text{ peak}}$  in nonburned children.

**LBM measurements.** On day 2 (6 mo and/or 9 mo), LBM measurements were made for all four burned groups and in the nonburned group by dual-energy X-ray absorptiometry (DEXA) by using the QDR 4500A software (Hologic, Waltham, MA). Although assessment of body composition was made at discharge, this is a time point at which some patients have staples or are undergoing fluid shifts in cellular and whole body water, due to resuscitation or excisional therapy, thereby confounding assessment of LBM (15). Therefore, LBM was not reported for the discharge time period. Scans were taken in slow-array mode, with the patient lying supine on the scanning table. The protocol for obtaining a whole body scan was done according to the manufacturer's instruction and has been described by our group (26). Briefly, DEXA with pediatric software was used to measure the attenuation of two X-ray beams, one high energy and the other low energy. These measurements were then compared with standard models of thickness used for bone and soft tissue. Subsequently, the calculated soft tissue was separated into LBM, bone mineral content, and fat mass. LBM is reported in kilograms.

**Fat-free mass measurements.** Assessment of fat-free mass (FFM) was performed by whole body potassium-40 scintillation counting method in a heavily shielded counting room with a low level of background noise, a <sup>32</sup>NaI detector array, and a computed data analysis method. This method has been previously validated in children (12) and corroborated in burned children with DEXA and stable isotope methods (18). The counting precision of the instrument used is within <1.5%, and it was calibrated daily by using a bottle manikin absorption phantom (Canberra Industries, Meriden, CT) with simulated fat overlays. FFM is reported in kilograms.

**Physical and occupational rehabilitation.** Children in the GH and Saline groups returned home to continue standard occupational and physical rehabilitation. The patient (parents or legal guardians) was instructed to continue standard OT or PT at home with or without supervision by an occupational or physical therapist. In contrast, children in the

GHEX and SALEX groups remained and received a supervised hospital-based OT/PT program and a structured exercise-training program. The OT/PT program for burned children included range-of-motion exercises, specific limb or digit position, and splinting. In addition, scar management with pressure therapy and inserts was used. Finally, patient and caregiver education of the described OT/PT program was done.

**Exercise training program.** All subjects were sedentary before starting the exercise program and had never participated in an exercise-training program. Children were considered sedentary if they did not participate in at least 30 min of exercise per day for 3 times/wk or were not engaged in organized sports. Each exercise training session consisted of resistance and aerobic exercises, with aerobic exercise preceding resistance exercise. Eight basic resistance exercises were used: bench press, leg press, shoulder press, biceps curl, leg curl, triceps curl, and toe raises. At no time did the GHEX and SALEX groups train using the Biodex dynamometer. All exercises were done by using variable-resistance machines or free weights. During the first week of training, the patients became familiarized with the exercise equipment and were instructed in proper weight lifting techniques. The weight or load lifted was set at 50–60% of their individual 3 RM and was lifted for 4–10 repetitions for three sets. During the second week, the lifting load was increased to 70–75% (3 sets, 4–10 repetitions) of their individual 3 RM and continued for weeks 2–6. After this, training intensity was increased to 80–85% (3 sets, 8–12 repetitions) of the 3 RM and implemented from weeks 7–12. A rest interval of ~1 min was given between sets.

Each exercise training session also included aerobic conditioning exercises on a treadmill or cycle ergometer. This aerobic training was carried out 3 days/wk. Each session lasted 20–40 min, and participants exercised at 70–85% of their previously determined individual  $\dot{V}O_{2\text{ peak}}$ . All exercise sessions were preceded by a 5-min warm-up period on the treadmill at an intensity of <50% of each individual  $\dot{V}O_{2\text{ peak}}$ . Heart rate and oxygen saturation were monitored by using a Radical Signal Extraction pulse oximeter (Masimo, Irvine, CA). Rated perceived exertion was obtained at regular intervals during aerobic exercise. All exercise sessions and exercise prescriptions were supervised by an exercise specialist and were conducted according to the guidelines set by the American College of Sports Medicine and the American

Academy of Pediatrics (2, 4). No strength training activities were permitted outside the supervised training session; however, both groups were allowed to pursue their normal daily activities. Patients randomized to the exercise program were required to have participated in at least 33 workout sessions of the 36 total workout sessions to be considered compliant with the exercise program.

**Nonburn children.** Sixteen healthy, nonburned children were recruited for assessment of muscle strength and body composition. Exercise testing was done in a similar fashion as done in burned children but only at a single time point. Additionally, none of the nonburned children participated in the 12-wk exercise program. Values obtained in nonburned children for muscle strength and lean mass are presented solely as reference and are not used in statistical analyses. In addition, none of the nonburned children received injections or underwent hormone analysis.

**Data analysis.** All data are expressed as means  $\pm$  SE. Baseline values and the mean percent change of the dependent variables due to different interventions were analyzed by using one-way ANOVA and a Student-Newman-Keuls test for multiple comparisons for the GHEX, SALEX, GH, and Saline groups before and after 12 wk of intervention. Descriptive statistics are given for age-matched, sedentary, nonburned children but are not included in ANOVA analyses. A  $P$  value < 0.05 was considered statistically significant.

## RESULTS

Data from 44 patients who were compliant with the exercise program and drug administration and had a complete set of data for all assessments are reported. The range in age for all four groups was 7–17 yr. Length of hospital stay was similar for all four groups ( $P = 0.813$ ), with a range of 14–61 days for the GHEX group and 8–57 days for the GH group. The length of hospital stay for the SALEX group was 8–83 days and for the SAL group was 13–81 days (Table 1).

There were no differences at 6 mo postburn between the groups in age, %total body surface area burned, vertical height, standing weight, and body surface area. At 9 mo postburn, all groups had similar levels in vertical height and standing weight. Additionally, body weight and vertical height remained relatively un-

Table 1. Demographic characteristics of participants

	GHEX		SALEX		GH		Saline	
<i>n</i>	10		13		10		11	
Gender								
Male	9		10		9		9	
Female	1		3		1		2	
%Burn (TBSA)	60.3 $\pm$ 1.9		58.5 $\pm$ 2.8		55.9 $\pm$ 3.1		53.4 $\pm$ 3.1	
LOS, days	31.4 $\pm$ 3.7		38.4 $\pm$ 4.8		30.1 $\pm$ 3.7		35.8 $\pm$ 4.6	
	6 Months		9 Months		6 Months		9 Months	
Age, yr	11.0 $\pm$ 0.8	11.3 $\pm$ 0.8	10.5 $\pm$ 0.7	10.8 $\pm$ 0.7	11.5 $\pm$ 1.6	11.8 $\pm$ 1.6	10.8 $\pm$ 0.7	11.1 $\pm$ 0.7
Height, cm	143.3 $\pm$ 6.0	143.3 $\pm$ 5.5	140.6 $\pm$ 6.3	143.7 $\pm$ 6.8	137.3 $\pm$ 1.5	138.3 $\pm$ 1.2	146.7 $\pm$ 1.4	147.4 $\pm$ 1.4
Weight, kg	50.5 $\pm$ 9.2	53.6 $\pm$ 9.7	38.1 $\pm$ 5.6	42.6 $\pm$ 6.4	38.6 $\pm$ 10.6	40.9 $\pm$ 11.2	36.6 $\pm$ 3.7	39.0 $\pm$ 4.1

Values are means  $\pm$  SE; *n*, no. of subjects. TBSA, total body surface area; LOS, length of hospital stay; GHEX, growth hormone and exercise; SALEX, saline and exercise; GH, growth hormone alone; Saline, saline alone. All 4 groups of burned children were similar in %TBSA, age, height, and weight at 6 mo postburn injury. Height and weight did not significantly change during the 12-wk study period. Note: the nonburned group of children ( $n = 16$ ) was not included in statistical analyses and is included as reference only. Mean  $\pm$  SE values for the nonburned group (9 males, 7 females) were as follows: age, 10.8  $\pm$  0.8 yr; height, 150.2  $\pm$  3.9 cm; weight, 50.0  $\pm$  3.6 kg.

changed at 9 mo postburn in all groups compared with 6 mo postburn.

LBM obtained by DEXA resulted in a mean percent increase of  $5.4 \pm 1.6\%$  in the SALEX and  $5.8 \pm 1.8\%$  in the GH groups after 12 wk of intervention, reflecting an effect of rHGH supplementation or exercise alone. When both rHGH and exercise were administered together (GHEX), the mean percent increase was  $9.0 \pm 2.1\%$ ; however, this increase was not significantly different from that of the SALEX and GH groups ( $P = 0.33$  and  $P = 0.21$ , respectively). As expected, LBM was relatively unchanged in the Saline group ( $-1.2 \pm 2.0\%$ ; Fig. 2A).

The FFM values were similar in all groups at 6 mo. Similarly to LBM, the mean percent change in FFM from 6 to 9 mo was not significantly different between groups ( $P = 0.46$ ; Fig. 2B). However, both mean percent changes in FFM and LBM had a similar pattern of response.

Strength significantly increased with exercise, as reflected by the mean percent increase in peak torque

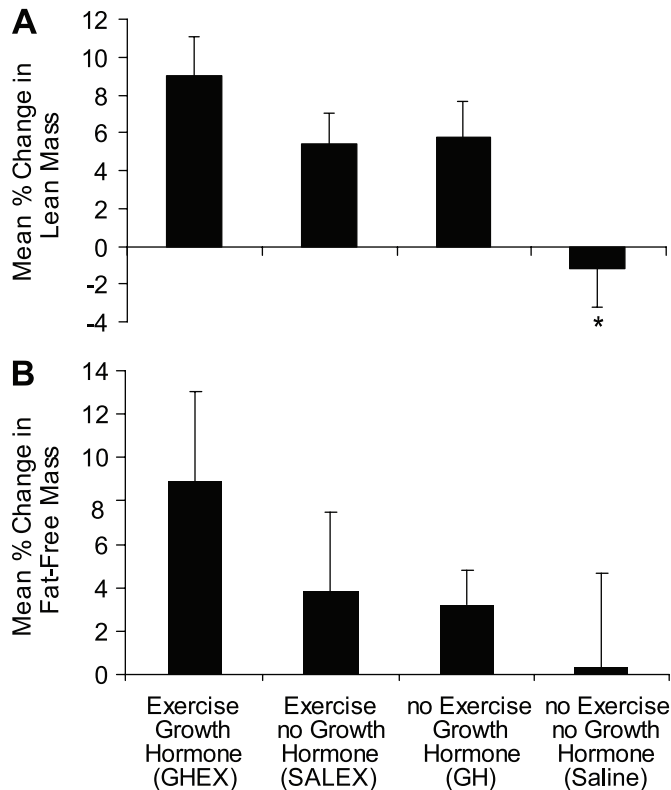


Fig. 2. A: mean ( $\pm$ SE) %change in lean body mass (LBM) after 12 wk of intervention. There were no significant differences in the mean %change between 6 and 9 mo in LBM among the GHEX ( $n = 10$ ), SALEX ( $n = 13$ ), and GH ( $n = 10$ ) groups. As expected, the mean %increase in LBM was greater in the GHEX, SALEX, and GH groups than in the Saline ( $n = 11$ ) group ( $*P < 0.05$ ). LBM (in kg) was used in the calculation of mean %changes. B: mean ( $\pm$ SE) %change in fat-free mass (FFM) after 12 wk of intervention. The mean %changes due to interventions were not statistically different in FFM among GHEX, SALEX, and GH groups. FFM (in kg) was used in the calculation of mean %changes. Values are from a subset of 28 out of a possible 44 children ( $n = 7$  for GHEX,  $n = 9$  for SALEX,  $n = 7$  for GH,  $n = 5$  for Saline).

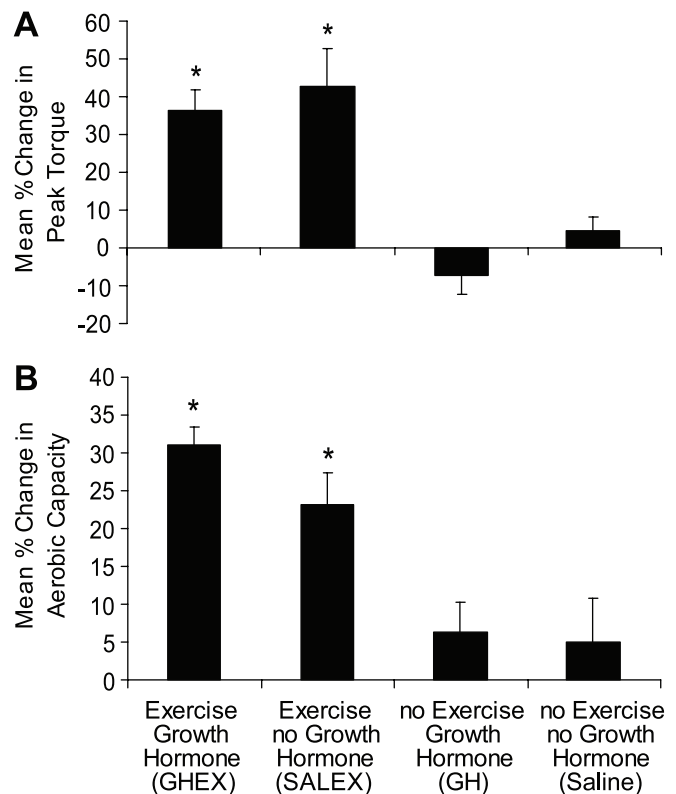


Fig. 3. A: mean ( $\pm$ SE) %change in knee extensor peak torque at 150°/s after 12 wk of intervention. \*Significant difference ( $P < 0.05$ ) in strength (reflected by peak torque) in the 6- to 9-mo mean %change between exercising (GHEX and SALEX) and the nonexercising groups (GH and Saline). Peak torque (in N·m) was used in the calculation of the mean %changes. B: mean ( $\pm$ SE) %change in relative peak oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ) after 12 wk of intervention in all 4 groups. \*Significant ( $P < 0.05$ ) difference in  $\dot{V}O_{2\text{peak}}$  between the exercising groups (GHEX and SALEX) and the nonexercising groups (GH and Saline), reflecting increased cardiovascular endurance. Relative  $\dot{V}O_{2\text{peak}}$  (in  $\text{ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was used in the calculation of %changes.

after 12 wk of exercise intervention, independent of drug delivered. The GHEX and SALEX groups increased  $36.2 \pm 5.4$  and  $42.6 \pm 10.0\%$ , respectively, and were not significantly different from each other ( $P = 0.58$ ). In contrast, lack of exercise training in the GH or the Saline groups did not significantly increase muscle strength ( $-7.4 \pm 4.7$  and  $6.7 \pm 4.4\%$ , respectively; Fig. 3A).

Similar to muscle strength, exercise independent of rHGH administration caused a significant mean percent increase in  $\dot{V}O_{2\text{peak}}$  of  $31.1 \pm 2.4$  and  $23.1 \pm 4.2\%$  in the GHEX and SALEX groups, respectively. In contrast, lack of exercise training did not cause a significant change in peak aerobic capacity of the GH or Saline groups (Fig. 3B). Mean values obtained for FFM, LBM, peak torque, and  $\dot{V}O_{2\text{peak}}$  at 6 and 9 mo are reported in Table 2.

The mean percent changes from 6 to 9 mo for trunk and arm lean mass were not significantly different between groups. Only the mean percent change in leg lean mass resulted in a significant increase in GHEX, SALEX, and GH compared with Saline. However, we

Table 2. *Body composition, leg muscle peak torque, and peak oxygen consumption results*

	GHEX (n = 10)		SALEX (n = 13)		GH (n = 10)		Saline (n = 11)	
	6 Months	9 Months	6 Months	9 Months	6 Months	9 Months	6 Months	9 Months
Lean body mass, kg	33.2 ± 3.9	36.9 ± 4.4	30.8 ± 3.9	32.6 ± 4.2	30.8 ± 5.1	32.3 ± 5.1	29.6 ± 3.4	29.3 ± 3.4
Lean trunk mass, kg	18.1 ± 3.3	19.4 ± 3.3	16.0 ± 2.3	16.4 ± 2.4	13.6 ± 3.3	13.6 ± 3.0	14.8 ± 2.0	15.1 ± 2.1
Lean arm mass, kg	5.28 ± 2.3	5.90 ± 2.3	2.82 ± 0.5	2.90 ± 0.5	2.73 ± 0.8	2.86 ± 0.8	4.34 ± 1.2	4.52 ± 1.2
Lean leg mass, kg	10.4 ± 1.9	11.6 ± 2.2	9.60 ± 1.4	10.4 ± 1.6	9.45 ± 2.2	10.1 ± 2.2	9.27 ± 1.5	9.53 ± 1.5
Fat-free mass, kg	29.5 ± 3.3	32.2 ± 4.2	25.8 ± 3.8	27.1 ± 4.6	21.2 ± 2.0	22.0 ± 2.2	28.7 ± 3.6	28.8 ± 3.6
Peak torque, N·m	32.9 ± 6.2	44.6 ± 8.4	25.9 ± 6.1	34.4 ± 8.0	31.4 ± 5.8	28.7 ± 5.8	32.8 ± 7.1	33.2 ± 7.2
Peak oxygen consumption, ml·kg <sup>-1</sup> ·min <sup>-1</sup>	28.1 ± 1.3	36.8 ± 2.0	29.1 ± 1.8	35.0 ± 1.4	31.0 ± 2.5	33.7 ± 3.0	28.6 ± 1.7	30.2 ± 2.5

Values are means ± SE; *n*, no. of subjects. All groups of burned children were similar in fat-free mass, lean body mass, peak torque, and peak oxygen consumption at 6 mo postburn injury. Statistical analyses of the mean %changes from 6 to 9 mo postburn injury in body composition and functional outcomes are presented in Figs. 2–4. Note: the nonburned group of children was not included in statistical analyses and is included as reference only. Mean (±SE) values for the nonburned children (*n* = 16) are as follows: lean body mass, 39.0 ± 2.4 kg; trunk lean mass, 18.0 ± 1.7 kg; arm lean mass, 4.73 ± 0.5 kg; leg lean mass, 13.0 ± 1.2 kg; peak torque, 76.9 ± 11.0 N·m; peak oxygen consumption, 44.9 ± 2.0 ml·kg<sup>-1</sup>·min<sup>-1</sup>. Assessment of fat-free mass was not done in nonburned children. Note: for fat-free mass, the no. of subjects used was less due to technical difficulties (*n* = 7 for GHEX; *n* = 9 for SALEX; *n* = 7 for GH; *n* = 5 for Saline).

could not demonstrate that GHEX, SALEX, or GH was significantly different from each other (Fig. 4).

The individual response in LBM to each intervention revealed that 10 of 10 children in the GHEX group and

10 of 13 children in the SALEX group had an increase in lean mass. Whereas, in the GH group, 6 of 10 children had an increase in lean mass. In contrast, only 3 of 11 children in the Saline group had an increase in lean mass. The individual responses in leg strength revealed that 10 of 10 and 12 of 13 children in the GHEX and SALEX groups, respectively, increased leg strength, indicating an exercise effect. In contrast, 5 of 11 children increased in strength in the Saline group, whereas 4 of 10 children in the GH group had an increase in strength.

Descriptive statistics on strength, lean mass, and aerobic capacity are reported for age-matched, nonburned children in Table 2. We have limited the analysis of nonburned children to descriptive statistics and have not included these in the ANOVA analysis, because the nonburned children were only evaluated at one time point.

Hormonal blood levels are presented in Table 3. Growth hormone and growth hormone-dependent biochemical marker (IGF-I, IGFBP-3) levels in all groups were statistically similar at discharge (*P* = 0.39, 0.82, 0.54 for rHGH, IGF-I, and IGFBP-3, respectively). At all time points, rHGH levels were independent of intervention. The mean percent change in IGF-I levels from discharge (starting point) to 9 mo postburn (end point) was similar for the exercise groups (GHEX and SALEX) and the GH group (*P* = 0.58 and *P* = 0.36 comparing GHEX vs. SALEX or GH, respectively). However, these mean percent changes were significantly different than the mean percent change in the Saline group (*P* = 0.02), reflecting an effect of exercise or effect of rHGH administration on IGF-I levels. Similar to rHGH, IGFBP-3 levels were not significantly different at discharge. In addition, the mean percent changes in IGFBP-3 levels from discharge to 9 mo postburn were not significantly different and were also independent of intervention. No side effects typically attributed to rHGH administration were noted in our study.

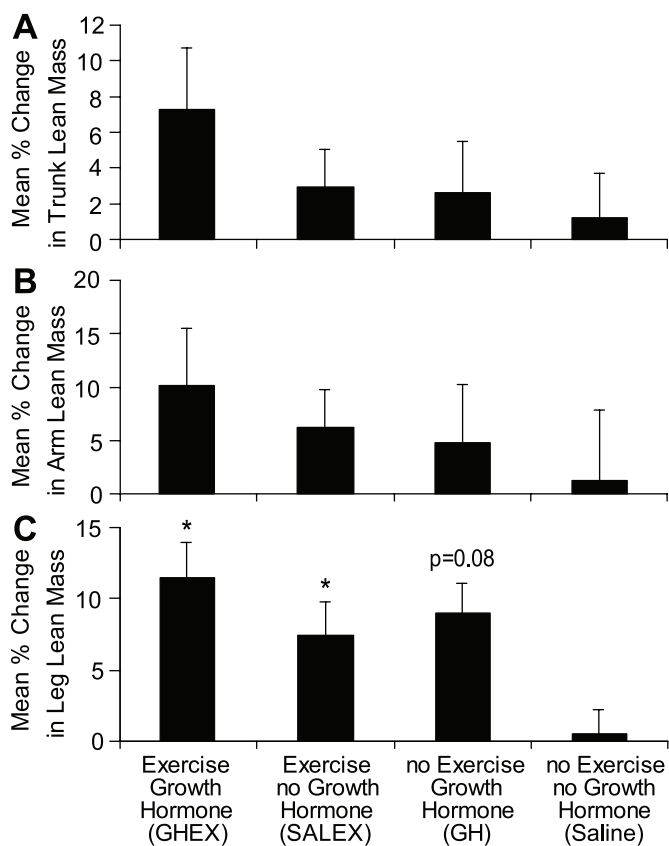


Fig. 4. Mean (±SE) %change in trunk (A), arm (B), and leg (C) lean mass after 12 wk of intervention. Lean mass (in kg) was used in the calculation of mean %changes. The mean %change in leg lean mass from 6 to 9 mo was not significantly different among GHEX, SALEX, and GH group. Not surprisingly, the mean %change in leg lean mass in the GHEX and SALEX was significantly greater than in the Saline group alone: \*GHEX and SALEX vs. Saline, *P* < 0.05. GH vs. Saline, *P* = 0.08.

Table 3. *Hormone levels at hospital discharge, 6 and 9 mo postburn injury*

	GHEX (n = 10)			SALEX (n = 13)			GH (n = 10)			Saline (n = 11)		
	DX	6 Months	9 Months	DX	6 Months	9 Months	DX	6 Months	9 Months	DX	6 Months	9 Months
rHGH, ng/ml	1.0 ±0.2	1.2 ±0.8	1.7 ±0.7	3.7 ±1.4	0.6 ±0.2	2.3 ±1.6	1.5 ±0.6	2.4 ±0.8	2.9 ±0.8	1.5 ±0.4	2.3 ±1.2	3.5 ±0.7
IGF-I, ng/ml	146.5 ±22.9	217.3 ±70.9	206.0 ±50.8*	126.1 ±33.6	250.1 ±44.4	271.6 ±55.2*	124.4 ±22.9	233.2 ±58.1	237.8 ±47.0*	159.0 ±41.5	136.8 ±27.4	154.6 ±35.7
IGFBP-3, ng/ml	2,358.7 ±286.2	3,604.0 ±100.3	3,788.3 ±347.8	2,553.7 ±338.8	2,964.3 ±410.8	3,364.0 ±398.1	2,123.0 ±220.7	3,689.1 ±409.8	3,612.0 ±215.5	2,626.6 ±324.1	3,350.4 ±397.9	3,425.4 ±333.8

Values are means  $\pm$  SE *n*, no. of subjects. Values are mean %change from hospital discharge to specific time point. DX, hospital discharge; rHGH, human growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor-binding protein-3. All 4 groups of burned children were similar in rHGH, IGF-I, and IGFBP-3 levels at hospital discharge ( $P = 0.39, 0.82, 0.54$ , respectively). The mean %change in IGF-I levels from discharge (start point) to 9 mo postburn (end point) were similar for the GHEX, SALEX, and GH. However, these mean %changes were significantly different than the mean %change in the Saline group ( $*P = 0.02$ ). Expected value range for rHGH is  $<10.0$  ng/ml (human growth hormone ELISA DSL-10-1900, Diagnostic Systems Laboratories, Webster, TX). Expected value range for IGF-I is 88–800 ng/ml and for IGFBP-3 is 1,160–6,000 ng/ml (source: IGF-I ELISA DSL-10-5600 and IGFBP-3 ELISA DSL-10-6600).

## DISCUSSION

The results of this study show for the first time that, in burned children, administration of rHGH, combined with a 12-wk exercise-training program, significantly increases LBM, but not to a significantly greater extent than rHGH alone or exercise alone.

These results are consistent with previous findings in the elderly and in young, nonburn male adults. Yarasheski et al. (42, 43) reported that administration of growth hormone in elderly men increased lean mass, but that, when growth hormone was combined with exercise, the increase in LBM was not enhanced further. They attributed this result to an increase in total body water content (42, 43). The administration of rHGH to nonburned children has been previously reported and also has been shown to increase LBM (14, 20, 32). Myers et al. (32) found an increase in LBM of  $\sim 10\%$  in 35 children (ages 4–16 yr) with Prader-Willi syndrome given  $0.18\text{--}0.3$  mg $\cdot$ kg $^{-1}\cdot$ wk $^{-1}$  of rHGH. In children with cystic fibrosis, rHGH administration increased LBM by 4% after 6 mo of treatment, whereas the placebo-treated group increased LBM by  $\sim 1.7\%$  (14, 20).

In addition, in burned children, the long-term administration (12 mo) of rHGH has been studied by Hart et al. (15). In their study,  $0.05$  mg $\cdot$ kg $^{-1}\cdot$ day $^{-1}$  of rHGH resulted in an increase of  $\sim 4.6\%$  in LBM compared with that in placebo-treated burned children. However, assessment of functional outcome was not reported. The increase in LBM in the SALEX, GHEX, and GH groups in our study are in agreement with the finding of Hart et al.

Our results demonstrating an increase in LBM in response to exercise in burned children are in agreement with previous studies (13, 30), including a recent report by our group (36), which showed an increase in LBM of 6.0% in response to exercise alone. Fukunaga et al. (13) showed an increase in muscle cross-sectional area of 5th graders, but not of 4th or 3rd graders, measured by the ultrasonic method in response to 12 wk of maximal sustained isometric exercise training.

Similarly, Merish and Stoboy (30) showed an increase in quadriceps cross-sectional area determined by nuclear magnetic resonance imaging in two prepubertal, monozygous twin boys in response to 10 wk of maximal sustained isometric training. Although our resistive exercise program differed in mode of training to that of Fukunaga et al. (13) or the studies of Merish and Stoboy (30), both studies support our finding of increases in LBM in burned children in response to resistive training. Our results of regional (trunk, arm, and leg) lean mass were similar to total body lean mass, where the mean percent changes in the GHEX, SALEX, or GH groups were not significantly different from each other.

To our knowledge, the present study is the first to report the effects of rHGH on muscle strength in burned children. Our study showed that improvement in muscle strength was not dependent on rHGH but rather on exercise training. This increase in muscle strength in response to exercise corroborates our previous finding in a separate group of burned children, which showed similar gains in leg peak torque (strength) (36). Although previous reports of strength gains in nonburned children showed a 13–30% improvement as a result of resistance training, those studies did not control for a learning effect and differed from our study in other factors, such as duration, intensity, frequency, and volume of training, as well as age of participants, types of weight lifting equipment used, and mode of testing used (isokinetic vs. isotonic) (8–10). As such, any substantive comparisons are not plausible.

In the present study, the beneficial increase in LBM due to growth hormone alone was not always accompanied by an increase in muscle strength. Only children involved in the exercise program (GHEX and SALEX) increased muscle strength. An increase in LBM in response to the administration of growth hormone alone has been generally found not to be related to improved muscle strength in the elderly and young adults (37, 41, 43, 44). For example, Lange et al. (28) reported an increase in FFM in response to growth

hormone administration alone; however, growth hormone administration alone had no effect on isokinetic quadriceps muscle strength (28). Furthermore, it is clear that, besides muscle mass, other factors, such as effort, motivation, neural recruitment, fiber-type affected, and mode of testing, are important in determining muscle strength.

In a previous report, Taaffe et al. (37) showed that an increase in lean mass did not result in an increase in muscle strength and attributed this to fluid retention and an increase in noncontractile protein. To account for the possibility that increases in body water might have confounded our lean mass findings, we used whole body potassium scanning before and after 12 wk of treatment. The mean percent change in FFM after 12 wk was similar to the mean percent changes in LBM ( $P = 0.645$ ), thus corroborating the results of our assessment of LBM via DEXA (Fig. 2). Unfortunately, due to technical difficulties and missed appointments, we could only test a subset of patients (28 of 44 children) using whole body potassium scanning; therefore, it cannot be completely ruled out that nonmuscle FFM gains (e.g., cellular and whole body water) did not occur in the GHEX or GH groups. No measures of the type of muscle protein being produced were made in our study to discern whether muscle protein produced was primarily contractile or noncontractile.

Another possibility for the dissociation between rHGH administration and increased strength is that the time period for which rHGH was given was not sufficient to increase strength, as previous studies have reported that increases in strength due to rHGH alone are seen only after 12 mo (5, 24, 25). In adults, when rHGH was given together with continued exercise for 10 wk, subsequent to a plateau in muscle strength gains due to a 14-wk exercise program alone, no further improvement in muscle strength was observed (37). It is not known if a similar response would occur or not in burned children. Therefore, we cannot exclude the possibility that longer term administration of rHGH would have resulted in improved muscle strength, although we believe this is unlikely.

How does LBM and leg strength in burned children compare with those in nonburned children? With the inclusion of a nonburned group, we are able to observe that the total amount of lean mass is not apparently different in burned children and nonburned children. This is probably due to the maintenance of a similar ratio of LBM to total body mass in the preburned, as well as in the postburn, stage. In other words, once burned, a child loses LBM as well as body mass (fat and bone), thus preserving the ratio of ~70–80% LBM. Specifically regarding muscle function (strength), the differences observed are more dramatic, as nonburned children exhibited peak torque values that were twice the values exhibited by burned children, even after 12 wk of exercise intervention (Table 2).

We initiated the exercise program at 6 mo postburn based on the 25 yr of clinical experience of the surgeons and the interdisciplinary team at our institution. At 6 mo postinjury, the majority of pediatric patients with

burns on >40% of their body surface are ambulatory and have had the opportunity to return home, placing them in a more favorable psychological disposition for another long-term institutionalization (e.g., 12 wk). In addition, we initiated long-term administration of rHGH on discharge from the hospital, when patient's wounds are considered to be 95% healed. Although burned children varied in the number of days in which they received rHGH, the average length of administration of growth hormone up to 9 mo postburn was ~238 days for the GHEX group and 240 days for the GH group (derived from length of hospital stay results). This represents a relatively negligible difference in days without rHGH, and we believe that the difference is not sufficient to prevent rHGH from exerting its effects on LBM at 9 mo postburn in the GH group vs. the GHEX group.

In conclusion, our results show an increase in LBM in burned children due to rHGH and exercise combined. However, we could not demonstrate that this increase was significantly greater than the observed increase in LBM with rHGH or exercise alone. In addition, we show that muscle strength significantly increases due to exercise training, independent of exogenous rHGH. As reflected in our results, severely burned children gain LBM and muscle strength by participating in an exercise program. We recommend that such a program be a fundamental component of multidisciplinary outpatient treatment for victims of thermal injury. However, the use of rHGH can also benefit burned children via an increase in LBM.

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