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Five-Year Outcomes after Oxandrolone Administration in Severely Burned Children: A Randomized Clinical Trial of Safety and Efficacy

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Abstract

Background—Oxandrolone, an anabolic agent, has been administered for 1 year post burn with beneficial effects in pediatric patients. However, the long-lasting effects of this treatment have not been studied. This single-center prospective trial determined the long-term effects of 1 year of oxandrolone administration in severely burned children; assessments were continued for up to 4 years post-therapy.

Study Design—Patients 0–18 years old with burns covering >30% of the total body surface area were randomized to receive placebo (n=152) or oxandrolone, 0.1 mg/kg twice daily for 12 months (n=70). At hospital discharge, patients were randomized to a 12 week exercise program or to standard of care. Resting energy expenditure (REE), standing height, weight, lean body mass, muscle strength, bone mineral content (BMC), cardiac work, rate pressure product (RPP), sexual maturation, and concentrations of serum inflammatory cytokines, hormones, and liver enzymes were monitored.

Results—Oxandrolone significantly decreased REE, RPP, and increased IGF-1 secretion during the first year after burn injury, and in combination with exercise significantly increased lean body

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mass and muscle strength. Oxandrolone-treated children exhibited improved height percentile and BMC content compared to controls. The maximal effect of oxandrolone was found in children aged 7–18 years. No deleterious side effects were attributed to long-term administration.

Conclusions—Administration of oxandrolone improves the long-term recovery of severely burned children in height, BMC, cardiac work and muscle strength; the increase in BMC is likely to occur by means of IGF 1. These benefits persist for up to 5 years post burn.

Keywords

Burn; oxandrolone; children; height; bone mineral content; hypermetabolic response; hypercatabolic response; resting energy expenditure

INTRODUCTION

Burn injury induces a hypermetabolic response that is characterized by elevations in cardiac work, metabolic rate, and muscle catabolism. Increased protein breakdown coupled with inadequate protein synthesis leads to muscle weakness and a loss of lean body mass (LBM). [1] Post-burn catabolic effects are not limited to muscle, as bone mineral content (BMC) and fat mass are decreased as well. This hypermetabolic response persists for up to 2 years after burn injury, greatly reducing the quality of life of severely burned patients. [2]

Oxandrolone, a synthetic oral non-aromatizable testosterone derivative, has only 5% of the virilizing activity and lower hepatotoxicity when compared to testosterone. Following administration, oxandrolone reaches peak serum concentrations within one hour and is excreted through the urine. Oxandrolone binds to androgen receptors in the skeletal muscle to initiate protein synthesis and anabolism. Because oxandrolone cannot be aromatized to estrogen, the likelihood of estrogen-dependent bone age advancement is reduced, making oxandrolone a safe therapeutic approach for growing children. [3–5]

In children with Turner's syndrome and other growth-related conditions, oxandrolone has been successfully for many decades to safely treat growth delays. [6–10] More recently, oxandrolone has been used to induce anabolism in patients experiencing muscle wasting associated with AIDS, major surgery, infections, malnutrition, neuromuscular disorders, or thermal injury. [11–12] Oxandrolone is the only androgenic steroid approved by the Food and Drug Administration to maintain body weight in these catabolic states. [3] These studies have demonstrated that oxandrolone has an excellent safety profile and is well tolerated by patients.

We have previously shown in severely burned children that short-term administration of oxandrolone during the acute phase of burn injury increases net muscle protein balance, maintains LBM, and shortens intensive care unit (ICU) stay. [1,13–15] Additionally, short term oxandrolone use was associated with elevation of liver enzymes aspartate aminotransrferase (AST) and alanine aminotransferase (ALT) from 17 – 40 days post burn. [13] Amino acid utilization was improved for up to 6 months post-burn in patients randomized to oxandrolone treatment.[16] In a small group of severely burned children, the administration of oxandrolone for 1 year post-burn increased LBM, BMC, muscle strength, heights, and weights. These benefits lasted for at least a full year after discontinuation of oxandrolone. [17–18] The addition of a 12-week exercise program to 1 year of oxandrolone therapy provided an even greater increase in weight and LBM. [19]

We conducted a single-center prospective randomized controlled trial in massively burned pediatric patients to investigate the effects of oxandrolone administration for 1 year post burn on growth, body composition, muscle strength, REE, liver and cardiac function, serum

markers, hormones, bone mass, and sexual maturation. We present the data from this trial, including data gathered up to 5 years post-burn to determine the safety and efficacy of the drug. A subset of these patients also underwent a 12-week exercise program to determine if exercise, in combination with oxandrolone, further affects LBM and BMC. These data are presented as well.

METHODS

Patients

Two thousand eight-hundred twenty one severely burned children were admitted to our institution from 2000 to 2010. Of these, 516 patients with burns over 30% of the total body surface area (TBSA) were consented and randomized to studies of various anabolic agents administered acutely and long-term post injury. Seventy patients were randomized to receive oxandrolone, 152 to the control group, and 294 to other ongoing studies (Figure 1). Control patients outnumbered oxandrolone-treated patients due to the balanced design of the randomization schedule, in order to share control subjects with all studies in a time contiguous fashion.

Patients 0–18 years of age at the time of the burn, with >30% of TBSA burned, and the need for at least one surgical intervention were included in the study. Exclusion criteria were the decision not to treat due to severity of the burn injury; anoxic brain injury; the presence of preexisting conditions such as HIV, AIDS, hepatitis, 5 year history of malignancy, or diabetes; and an inability to obtain informed consent. The administration of oxandrolone was started within 48 hours after the first operation and given orally at a dose of 0.1 mg/kg twice a day for one full year (BTG Pharmaceuticals, Iselin, NJ). Four Patients over 50 kg received 5 mg twice daily. Patients were assessed at admission; during acute hospitalization; at discharge; at 6, 9, 12, 18, and 24 months after burn; and annually thereafter. Patients who withdrew from the study were included in the data analysis up to the time of the withdrawal. This study was part of a large clinical trial (www.clinicaltrials.gov, NCT00675714) evaluating the outcomes of burn survivors after administration of therapeutic agents such as oxandrolone, propranolol, insulin, and the combination of oxandrolone and propranolol. Informed written consent approved by the Institutional Review Board of The University of Texas Medical Branch (Galveston, TX) was obtained from a legal guardian before enrollment in the study. Children older than 7 years assented to participate. This study adhered to ethical standards set forth by the Declaration of Helsinki (1975, revised 1983–2008).

Nutritional Support

Patients were resuscitated at admission according to the Galveston formula (a total of 5,000 ml/m^2 TBSA burned + 2, 000 ml/m^2 TBSA lactated Ringer's solution given during the first 24 hours). Within 48 hours of admission, all patients underwent burn wound excision and autograft / allograft application. After excision and grafting procedures, patients remained on bed rest for 3 days and then ambulated daily thereafter until the next procedure. Sequential staged excision and grafting were performed until the wounds healed.

Each patient received Vivonex TEN® enteral nutrition composed of 82% carbohydrate, 15% protein, and 6% fat, by nasoduodenal tube. During the first week of hospitalization, intake was calculated to deliver 1,500 $kcal/m^2$ TBSA + 1,500 $kcal/m^2$ TBSA burned. The dietary replacement was then modified after the first week of treatment to 1.4 times the resting energy expenditure (REE) (see Indirect Calorimetry below). Caloric intakes remained constant throughout hospitalization. Albumin, pre-albumin, and retinol-binding protein served as indicators of nutritional status during the acute hospitalization period. Parents

received nutritional counseling from the hospital nutritionist prior to discharge. In the outpatient setting, the patient's caretakers were interviewed regarding intake every day when the patient returned to the tub room, weekly while the patient remained in apartments and residencies in the hospital vicinity, and during each long term follow-up visit. After discharge from the ICU, patients received the commercial formula Boost® (Nestle Health Care Nutrition, Nestlé S.A., Vevey, Switzerland), which is composed of 41 grams of carbohydrate, 10 grams of protein, and 4 grams of fat, three times per day. Supplementation continued until the nutritionist confirmed that the regular diet met the patient's caloric requirements.

Patient Demographics and Injury Characteristics

Patient age, sex, and injury characteristics including the size and depth of the burn were recorded at the time of admission. Age-appropriate diagrams were used to determine burn size. [20] Conditions such as inhalation injury, sepsis, morbidity, and mortality were also recorded during the acute hospitalization. Inhalation injury was diagnosed by confirmation of the presence of soot, charring, mucosal necrosis, airway edema, or inflammation during fiber optic bronchoscopy, which was performed on all patients 24 hours after admission. Chest scintiphotograms, estimation of extra vascular lung water, and measurements of serum carboxyhemoglobin were also used for diagnostic purposes.

Indirect Calorimetry

All patients underwent weekly REE measurements during their acute hospitalization using the Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA). Studies were performed while the patients were asleep between midnight and 5 AM. Inspired and expired gas compositions were sampled and analyzed at 60-second intervals. Values for carbon dioxide production and oxygen volume consumption were recorded when they were at a steady state for 5 min. Measured values were compared with predicted normal values based on the Harris-Benedict equation and body mass index (BMI). [21–23]

Anthropometric Measures

Measurements of height and body weight were obtained at admission, throughout the acute stay, and at all follow-up visits out to 5 years post injury. A standard calibrated scale was used to measure body weight. A wall-mounted stadiometer was used to measure height to the nearest 0.1 cm. Height and weight percentiles were calculated using growth charts specific for age and sex (obtained from the Centers for Disease Control and Prevention or National Center for Health Statistics, respectively). [24] Percent change in height- or weight- for-age percentiles was used to compare and interpret the results.

In order to eliminate seasonal differences in growth between children, height and weight velocities were calculated as whole year increments. Percentiles for those individual increments were obtained for age to determine whether the growth rate was within normal ranges. Maximal yearly height gains were used to determine annual height velocity for each patient, which were then plotted on standard and gender-specific growth velocity charts [25] at 1, 2, 3, 4, and 5 years post burn. In addition, the percentages of patients with growth velocities more than two standard deviations (SDs) below the mean (<3rd percentile) were determined at each time point.

Body Composition

Dual energy x-ray absorptiometry (DEXA) was used to measure whole body fat, LBM, BMC, and bone mineral density (BMD) (QDR-4500W Hologic, Waltham, MA). Calibration was performed daily using a spinal phantom in the lateral, anteroposterior, and single beam

modes. A tissue bar phantom was used to calibrate individual pixels to accurately identify air, lean mass, bone, or fat. [26]

Measurement of Hormones, Proteins, and Cytokines

Blood and urine were collected from each patient for analysis of hormone, protein, liver enzyme, and cytokine levels at admission; during the acute stay; at discharge; and at follow-up appointments. Blood was collected in serum-separator collection tubes and centrifuged for 10 minutes at 1,320 rpm. The serum was removed and stored at −80°C until assayed. IGF-I, IGFBP-3, testosterone, parathyroid hormone (PTH), osteocalcin, albumin, and total protein were determined using HPLC and ELISA as previously published. [27–29] The Bio-Plex Human Cytokine 17-Plex panel was used with the Bio-Plex Suspension Array System (Bio-Rad, Hercules, CA) to profile expression of the following seventeen inflammatory mediators: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony stimulating factor, interferon-γ, monocyte chemoattractant protein-1, macrophage inflammatory protein-1β, and tumor necrosis factor. The manufacturer's protocol was followed as previously published. [27–29] Catecholamines were measured as previously published. [27–29]

Cardiac and Liver Measures

Heart rate (HR), stroke volume (SV), cardiac index (CI), mean arterial pressure (MAP), and cardiac output (CO) were determined for each patient. Cardiac and liver ultrasound measurements were made with a HP SONOS 100 CF echocardiogram (Hewlett Packard Imaging System, Andover, MA) equipped with a 3.5-MHz transducer. M-mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long axis position, and measurements were performed according to the American Society of Echocardiography recommendations. Stroke volume and CO were calculated using left ventricular end-systolic and end-diastolic volumes measures. Rate pressure product (RPP) was obtained as a correlate of the myocardial oxygen consumption by multiplying Mean Arterial Pressure (MAP) × HR. The MAP was obtained by continuous arterial monitoring during the ICU stay, and RPP was calculated during the long term period using blood pressure measurements obtained at each follow up visit. The liver was scanned using an Eskoline B-scanner, a modified HP diagnostic sounder 7214A, and a modified 3.5-MHz transducer probe. Liver size and weight were calculated using a previously published formula. [30] Measurements were performed during the acute stay and at follow-up time points.

Rehabilitation Program

Because we have previously shown that completion of an exercise program improves LBM, muscle strength, and cardiovascular function, patients aged 7–18 years were also randomized to receive the standard of care (SOC) or to participate in an exercise program within 6 months of discharge per our published protocol. [31] The SOC consisted of a home based physical and occupational therapy instructions without exercise. The exercise program consisted of 12 weeks of in-hospital, supervised, and individualized aerobic and resistance exercise training carried out five days a week in addition to standard occupational and physical therapy regimens. Aerobic conditioning exercises were performed on a treadmill or cycle ergometer five times a week. A standardized treadmill exercise test was conducted using the modified Bruce protocol to assess cardiovascular fitness and peak aerobic endurance time. Patients exercised at 70% to 80% of their previously determined peak aerobic capacity (VO_2 peak). Patients also performed resistance exercises such as bench press, leg press, and leg curls three times a week. Strength assessments were performed using the Biodex System 3 dynamometer (Biodex Medical Systems, Shirley, NY) according to instructions provided by the manufacturer. Peak torque values were calculated with the

Biodex software system and were corrected for gravitational movements of the lower leg and the lever arm.

Additional Measurements

At each follow-up time point, X-rays of the patient's hand and knee were obtained for bone age assessments and monitoring of the closure of the epiphyseal plate. In addition, psychosocial function was assessed at each follow-up time point. Patients participated in a structured clinical interview and were administered several self-report inventories.

Statistical Analysis

The distribution of the data was evaluated using QQ plots and the Kolmogorov-Smirnov normality test. Normally distributed data are presented as the mean ± standard deviation (SD) or standard error of the mean (SEM). Non-normally distributed data (*i.e.*, cytokines) are presented as the median ± median absolute deviation (median±MAD). Frequency data are expressed as counts or percentages. We did not control for differences between the groups in sex, age, or weight, except in the case of muscle strength, which is corrected for body weight. Two-sided equal-variance t-tests were used to compare normally distributed continuous data. All trends in the data were calculated using the loess smoother. [32] Standard errors were calculated using the loess functionality in R. To test for differences between the curves, we calculated and tested the maximum t-statistic using the permutation distribution. [33] A step-down procedure was used to adjust the family-wise error rate. [34] Two-sided Wilcoxon exact tests were used for non-normally distributed. Repeated measures Friedman's test was used to determine differences between intervals; if a difference were detected, a post hoc pairwise multiple comparisons (Dunn's) test was also performed. SAS (version 9.2) was used for data analysis and hypothesis testing. Fisher's exact test was used for frequency data. P values less than 0.05 were considered significant.

RESULTS

Patient Disposition and Demographics

Of the 222 patients enrolled in this study, 29 were lost to follow-up (control, n=20; oxandrolone, n=9), and 39 withdrew from study participation (control, n=28; oxandrolone, n=11). Demographics did not differ significantly between the oxandrolone and control groups (Table 1). Two-thirds of the patients were male, which is typical of burn injury in children. Almost half of the patients in each group were diagnosed with inhalation injuries. The length of hospital stay was approximately a half day per percent TBSA burned for patients in both groups. Mortality was low in both groups. No differences were noted in the number or time between operations when comparing the oxandrolone and control groups. Thirty-five patients participated in a 12-week exercise program during the rehabilitation period (control, n=21; oxandrolone, n=14), and 187 patients received SOC (controls n=131; oxandrolone n=56).

Indirect Calorimetry

Oxandrolone significantly decreased percent of predicted REE (P<0.01), and this effect was sustained until approximately 6 months post burn, indicating that hypermetabolism was significantly decreased. Although REE decreased over time in both groups, these values remained elevated for over 12 months after burn in the control group (Figure 2).

Anthropometric Measures

In the control group, the percentage of children below two standard deviations (SDs) of the mean for height velocity was 48% at 1 year post burn; 32% at 2 years post burn; and ~20%

at 3, 4, and 5 years post burn (Table 2). In the oxandrolone group, the percentage of patients falling more than two SDs below the mean for height velocity was only 8% at 1 year post burn and 7% at 2 years post burn. These values were significantly lower than those in controls (Table 2); however, this difference was not significant at 3, 4, or 5 years post burn.

Patients in the oxandrolone group exhibited a positive percent change in height percentiles at 1 year post burn, with a maximal change of ~40% seen at the second year (Figure 3A). These changes were significantly higher than those seen in controls at corresponding time points. In contrast to oxandrolone-treated patients, controls exhibited a negative percent change in height percentiles that was maximal at 1 and 2 years post burn, and these values remained negative at all time points. No significant differences were detected between groups at 3, 4 and 5 years post burn. As shown in Figure 3B, the effect of oxandrolone was maximal in children between the ages of 7 and 18 years, and the percent change in height percentile was significantly different up to 4 years post burn ($P<0.05$). Controls, on the other hand, showed a loss in height percentile over time.

An analysis of the percentage of children with weight velocities more than two SDs below the mean revealed that this percentage was lower in the oxandrolone group than in the control group at 1 year post burn, but not at 2, 3, 4, or 5 years post burn (Table 2).

Body Composition

Oxandrolone-treated patients who were 7–18 years old at the time of the injury had a significantly higher percent change in BMC than their control counterparts, beginning 2 years after injury and lasting until 5 years post burn ($P<0.001$) (Figure 4). No significant differences were detected between groups for children less than 7 years of age. Significant differences in BMC were also seen between children who received oxandrolone and participated in the exercise program and exercising control patients ($P<0.01$). BMD did not significantly differ between oxandrolone-treated patients and controls, regardless of age (data not shown). LBM approached significance at all time points ($P=0.06$). However, significance was reached only in exercising, oxandrolone-treated children, with differences between this group and exercising control patients at 2 years post burn, remaining significant throughout the remainder of the study period ($P=0.01$) (Figure 5B). No significant correlation was detected between percent change in LBM and percent change in BMC at any time post burn.

Hormones, Proteins, and Cytokines

Although catecholamines were elevated by burn injury, there were no differences between the groups. Serum constitutive proteins, pre-albumin, retinol-binding protein, and transferrin were significantly higher in oxandrolone-treated patients than controls from 2 to 12 months after burn injury (Figure 6 J, L, M). Serum albumin and total protein remained within normal limits and were not significantly different between groups (Figure 7D, H). Acute-phase proteins were significantly elevated in both groups during acute hospitalization (Figure 6). Complement C3 was markedly increased in the control group when compared to the oxandrolone group from discharge until 6 months post burn. Haptoglobin levels were significantly elevated in both groups until 6 months post burn, with oxandrolone-treated patients showing significant differences for 1 year following discharge when compared to controls. No differences were detected between the groups in α-2 macroglobulin and free fatty acid levels. In both groups, levels of C-reactive protein and α-1 acid glycoprotein returned to normal levels by 6 months after burn injury.

Confirming previous studies [2, 13, 35], IGF-1, IGFBP-3, testosterone, growth hormone, β-estradiol, and total T4 levels were decreased after injury (Figure 6). Oxandrolone induced

significant positive and persistent up-regulation of IGF-1 (Figure 6E); IGF-I was significantly higher in the oxandrolone group than the control group from discharge to 2 years post burn, with no differences in IGFBP-3 between the groups (Figure 6F). Exercise did not alter IGF-1 levels. Serum i-PTH and osteocalcin levels were dramatically decreased in both groups compared to normal values for over 2 years post burn and did not significantly differ between the groups (Figure 6P, Q). Free thyroid index and T3 uptake remained constant over time and did not differ between the groups (Figure 6B, C). Free T4 was significantly higher during the acute period in the oxandrolone group, although free T4 levels fell within normal range. Progesterone was consistently elevated in both groups but was not significantly different between them. All blood chemistry values were within normal limits, and no differences between the groups were detected. As in previous studies, [2, 36] glucose and insulin levels were above normal limits during acute hospitalization in both groups, with no significant differences detected between oxandrolone-treated and controls.

At most, serum cytokine levels significantly differed between the two groups at one or two time points after burn injury. These alterations were not sustained; therefore the overall inflammatory response did not differ between the groups.

Cardiac and Liver Changes

Absolute and percent of predicted CO, SV, and HR as well as CI and RPP were assessed up to 2 years following burn injury (Table 3). At 1 year post burn, CO, percent of predicted CO, and percent of predicted HR were significantly lower in the oxandrolone group compared to the control group ($P<0.05$). A significant decrease in RPP was observed in the oxandrolone group up to 1 year post burn ($p<0.05$). At 2 years post burn, percent of predicted CO and HR were significantly lower in the oxandrolone group than in the control group ($P<0.05$ for both). Liver length and weight were not significantly different between the control and oxandrolone groups (Table 3).

Rehabilitation Program

Significant increases in LBM, BMC, and muscle strength were seen in the oxandrolone + exercise group when compared to the control + exercise, control + SOC, or the oxandrolone + SOC groups. These effects persisted for up to 5 years post burn (Figure 5). Muscle strength, expressed as peak torque/kg body weight, was significantly greater in the oxandrolone + exercise group than the control + exercise group, the control + SOC group, or the oxandrolone + SOC group ($P<0.05$) at 9, 12, 18, and 24 months post burn. No significant difference in muscle strength was detected between oxandrolone + SOC and control + SOC.

Safety Profile

Our patients were closely monitored for adverse events for up to 1 year after discontinuation of oxandrolone. Thereafter, patients were assessed during annual follow-up visits. No signs of virilization were noted. Three female patients who had perineal burns developed clitoral hood edema, which resolved within 3 months. Chi-Square analyses revealed that oxandrolone did not affect acute and long-term psychosocial outcomes, including the prevalence of post-traumatic stress disorder, general anxiety, and depression between groups. Monitoring of liver and renal function included measures of serum creatinine, BUN, total protein, liver enzymes, total bilirubin, liver size, and liver weight (Table 3) (Figure 7). Alanine aminotransaminase and gamma glutamyl transpeptidase were elevated during the acute period in the control and oxandrolone groups, returning to normal levels 3 to 6 months post burn. However, levels of constitutive proteins were significantly increased in the oxandrolone group, indicating that liver function was not affected. The control group showed significantly higher levels of serum creatinine, total bilirubin, and BUN during the

acute period than the oxandrolone group. Although these values were statistically significant, some fell within normal ranges. Alkaline phosphatase and total protein tended to increase with time in both groups and were not different between the groups. The rest of the parameters did not differ between the groups at any of the time points. There was no significant advancement in bone age versus chronological age over the post burn observation period, and no difference between oxandrolone-treated patients (0.93±0.16) and controls (0.94±0.24) was detected.

DISCUSSION

Advances in burn care over the past several decades have dramatically decreased mortality, [37] leading to multiple challenges in long-term care of the burned victim, ranging from wound healing and hypertrophic scarring to physical disabilities and psychosocial difficulties. Burns covering over 30% TBSA are associated with a continuous hypermetabolic response that lasts for 2 years following the initial insult. [2, 21–22, 35] This was confirmed by our study, in which the control group showed a dramatic increase in REE during the convalescent period that remained above normal levels for as long as 18 months after burn. The present study revealed clear differences in the percent of predicted REE between oxandrolone and control patients up to 6 months after burn injury, indicating a sustained attenuation of the hypermetabolic state by oxandrolone. In this study, we have demonstrated that this prolonged attenuation of the hypermetabolic response is accompanied by long-term improvements in total body BMC and increased height velocity in massively burned children.

Severe burn is associated with marked retardation of linear growth and abnormal bone loss in the pediatric population. [38–39] Since the beginning of the 1960s, oxandrolone has been safely administered to pediatric patients with growth retardation. In 1965, a randomized controlled trial conducted by Ray and colleagues revealed that children with Down's syndrome exhibited significant improvements in height after oxandrolone treatment for 1 and 2 years at a dose of 0.5 and 0.25 mg/kg respectively. [7, 9] In 1965, Danowski reported that administration of 10–40 mg oxandrolone for 13–37 months induced a two-fold acceleration in height in children 3–17 years old who were below the third percentile for height. [6, 10] The use of oxandrolone in patients with Turner's syndrome as an adjunctive therapy to prevent constitutional growth delay has been well described. A randomized, double blind, placebo-controlled trial following a large cohort of girls with Turner's syndrome receiving growth hormone over a 10-year period showed that 0.05 mg/kg/day oxandrolone improved final height in these individuals. [8]

In this study, we were interested in examining the patients with growth arrest, as seen by height velocities below normal limits. Our data showed that a much larger percentage of patients with significant growth arrest were present in the control group than in the oxandrolone group (48 *vs.* 8%, $P<0.01$), similar results were found at the second year post burn (32 vs. 7%) ($P<0.05$).

We have previously shown that oxandrolone significantly improved growth in severely burned children after 1 year of treatment, with this increase maintained a full year after discontinuation of therapy. [18] This finding is supported by the current study, which revealed that oxandrolone-treated patients went from their baseline height percentile to higher ones, while control patients exhibited a loss in height percentile. This was more pronounced in children who were 7–18 years of age at the time of the burn injury, with oxandrolone-treated children in this age range having a significantly increased percent change in height percentiles for up to 4 years post burn. Importantly, these increases in height were associated with improvements in BMC, as assessed by DEXA. This study was

not powered to determine ultimate height in these severely burned children. Therefore, a larger study in a larger group of individuals to look at ultimate stature is necessary.

Bone loss occurs quickly following a severe burn, as manifested by an approximate 2% loss of total body BMC by 2 months post burn, increasing to about 3.5% by 6 months, with lumbar spine BMC falling about 8% and remaining low for up to 24 months post burn. [39] The recovery of bone from the catabolic effects of burn injury occurs relatively slowly. In previous studies of small groups of children, we have shown that a significant increase in BMC occurs at 12 months post burn. [17–18] Our study extends these observations by showing that oxandrolone continues to increase BMC for up to 5 years. In this study, we have provided evidence of a gradual increment in bone mass that reaches and remains significant after 2 years post injury. We speculate that this long-term increase in BMC results from the significant increase in IGF-1 levels as well as the protective effect of oxandrolone during the first year after burn, where ongoing stress and inflammation results in increased endogenous glucocorticoid production, abnormal calcium metabolism, and resorptive cytokine stimulation. The normal circulating levels of the chief binding protein for IGF-1, IGFBP3, could suggest an increase in IGFBP5, the main binding protein that transports IGF-1 to bone. [40] Interestingly, this effect is most pronounced in patients who were 7–18 years old at the time of the burn. This 2-year peak in BMC and height seen in oxandrolone-treated patients represents the beginning of the pre-pubertal growth spurt. The temporal aspect of changes in height percentiles seen here suggests that oxandrolone stimulates rather than impairs epiphyseal cartilage proliferation, possibly triggering ossification at these sites. *In vitro*, oxandrolone can up regulate the androgen receptor and concomitantly stimulate human osteoblasts to produce a significant but modest increase in type I collagen, alkaline phosphatase, and osteocalcin. These data suggest that there may be a weak direct effect of oxandrolone on osteoblasts. [41] However, burn victims have little to no osteoblastic activity from 14 days post burn to 1 year post burn. [42–44] As previously reported, oxandrolone had little to no effect on BMD. [17] However, the addition of exercise to oxandrolone therapy led to a significant increase in BMC concomitantly with an increase in LBM. This finding, as well as the finding that oxandrolone stimulates IGF-1, suggests that an increase in LBM brought about by oxandrolone and exercise could increase skeletal loading and in this particular setting, further increasing bone formation and BMC.

Severe burns accelerate catabolism of skeletal muscle. Previous studies have clearly shown that short-term oxandrolone treatment during the acute phase significantly increases LBM and net balance of muscle protein. [1, 13–15] Oxandrolone appears to achieve these effects by enhancing the efficiency of muscle protein synthesis. [1, 15] In previous studies, we have shown an improved net deposition of leg muscle protein through increased amino acid utilization after 6 months of oxandrolone treatment, [16] and significant improvement in LBM after 1 year of oxandrolone treatment.[17–18] Here, we found only a trend ($P<0.06$) toward improved LBM throughout the time studied.

The combination of a 12-week exercise program with oxandrolone therapy increased LBM to levels above that seen with oxandrolone therapy alone. Significant effects on muscle strength (measured by peak torque) were recorded only in the oxandrolone and exercise group. These results agree with our previous finding that combining exercise with oxandrolone produces more significant effects on LBM and weight gain. [19] The current findings are notable in that they show that the benefits of exercise are maintained for years after burn injury. In contrast, exercise seems to have little or no effect in BMC. This in agreement with a previous study where we evaluated the long-term effect of growth hormone, and found no effect in BMC in patients who participated in a similar exercise program. [45]

Oxandrolone and exercise probably affect body composition through different mechanisms. As already mentioned, oxandrolone likely increases total body BMC through IGF-1. However, the failure of oxandrolone and exercise to increase IGF-1 to significantly greater levels than oxandrolone alone suggests that the exercise effect is not mediated by IGF-1. The increase in LBM with exercise and oxandrolone suggests that the increase in BMC is secondary to increased skeletal loading, an effect different from that of IGF-1.

Assessment of cardiac function revealed that the oxandrolone group exhibited significant decreases in CO, percent predicted CO, percent predicted HR, and RPP at 1 year post burn as well as significant decreases in percent predicted CO and HR at 2 years post burn compared with the control group. These findings provide new evidence in favor of a more efficient utilization of energy by the myocardium of patients who received oxandrolone. Interestingly, these findings coincide with the increases seen in height and BMC during the same time period, suggesting that an attenuation of the hypermetabolic response occurred in oxandrolone-treated patients while the controls remained hypermetabolic. Considering the marked contributions by the heart to the overall daily energy expenditure, we speculate that the effect exerted by oxandrolone on cardiac physiology could explain the decrease in percent predicted REE as measured by indirect calorimetry. Additional studies are needed to further elucidate the mechanism by which oxandrolone decreases REE.

Special attention has been given to sex as a predictor of outcome following injury. Controversies have arisen regarding whether administration of androgens or estrogens can positively impact outcomes. Differential effects of sex hormones on immunity, organ function, and cellular response have been reported and continue to be extensively investigated. [46–50] We found that the effect of oxandrolone on height velocity was the same in females and in the overall group. The positive effect in girls persists alongside that seen in boys.

Assessment of safety showed that there were no long-lasting deleterious effects associated with oxandrolone use in our patients. Three female patients with perineal burns developed clitoral hood edema, and this condition was resolved within 3 months of discontinuation of treatment. Although we previously reported an elevation of AST and ALT between 17 and 40 days post burn in patients treated with oxandrolone, here we show that there are no long-term elevations in these markers. Bone age was not affected; premature closure of the epiphyses was not found. Anxiety, pain and mood disorders were not different between the groups. Taken together, this data indicate that oxandrolone can be safely used in severely burned children.

In conclusion, our findings provide strong evidence that oxandrolone is efficacious in attenuating the hypermetabolism elicited by burn injury, significantly improving the long-term recovery of severely burned children in height, bone mineral content, and muscle strength. This, taken with the safety profile of this drug, supports the use of oxandrolone as an adjunct therapy to the current standard of burn care.

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ABBREVIATIONS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AIDS	acquired immune deficiency syndrome
BMC	bone mineral content
BMD	bone mineral density
CI	cardiac index
CO	cardiac output
DEXA	dual energy x-ray absorptiometry
HR	heart rate
LBM	Lean body mass
MAP	mean arterial pressure
PTH	parathyroid hormone
REE	resting energy expenditure
RPP	rate pressure product
SD	standard deviation
SEM	standard error of the mean
SOC	standard of care
SV	stroke volume
TBSA	total body surface area

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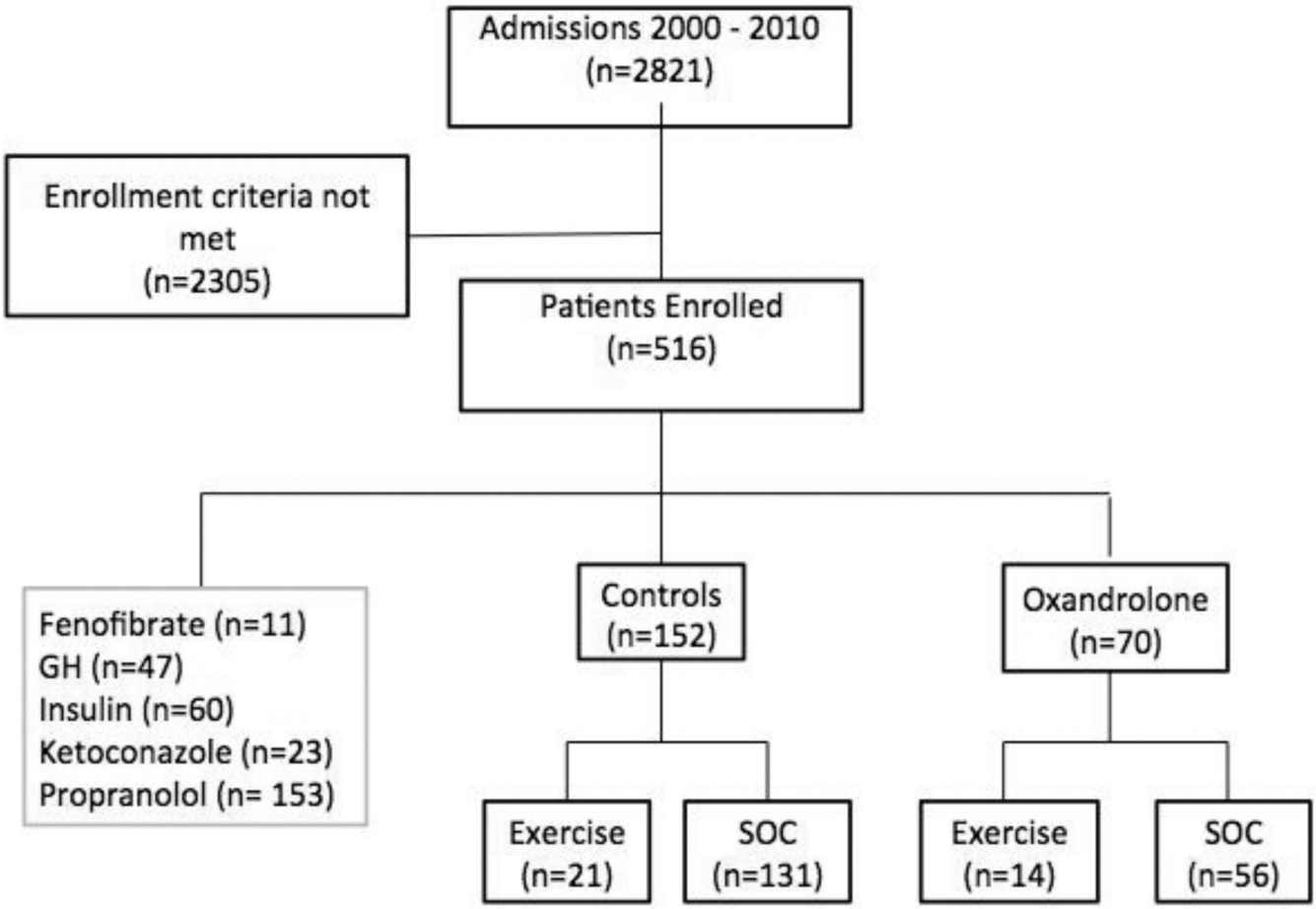

FIGURE 1.
Consort diagram.

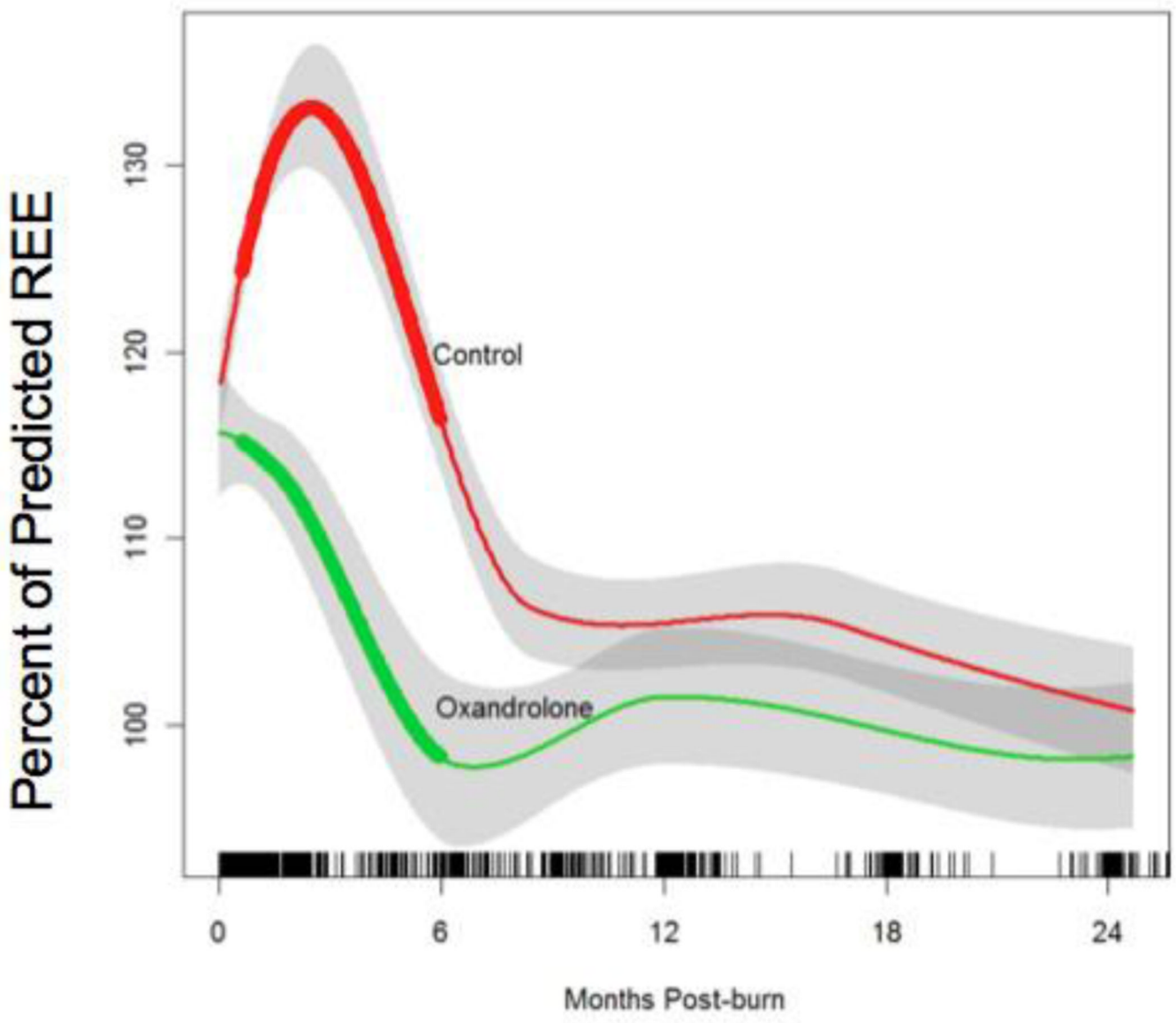

FIGURE 2.

Effect of oxandrolone on percent predicted resting energy expenditure. Data are represented the loess-smoothed trend in resting energy expenditure (REE) with shading indicating +/− standard error. Hatch marks across the bottom represent the density of sampled data at each time point (1,427 total observations). Time points at which differences are significant are indicated with wider lines ($p<0.004$).

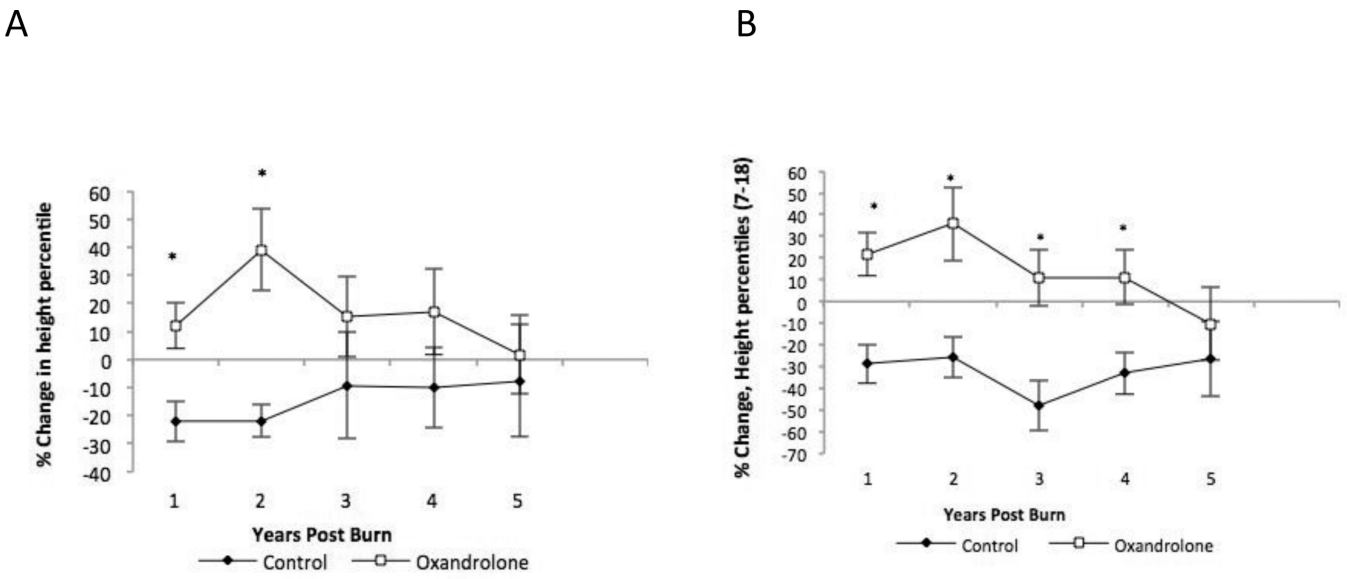

FIGURE 3.

Percent change in height percentile from 1 to 5 years post burn in (A) all patients and in (B) patients aged 7–18 years. Data are expressed as mean ± SEM. *p<0.05 vs control.

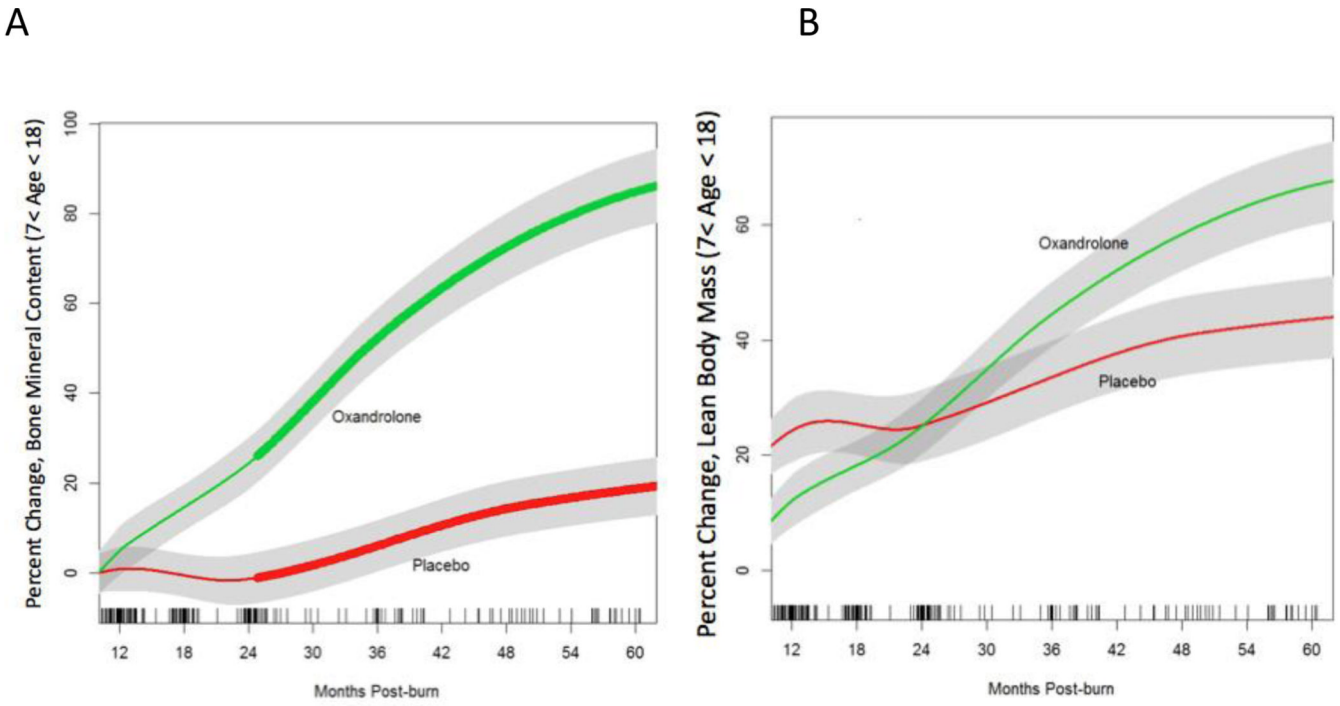

FIGURE 4.

Percent change in (A) total body bone mineral content and (B) lean body mass. Data are represented as the loess-smoothed trend in BMC and in LBM with shading indicating +/− standard error. Hatch marks across the bottom represent the density of the sampled data at each time point (572 total observations). Time points at which differences are significant are indicated with wider lines ($p<0.001$).

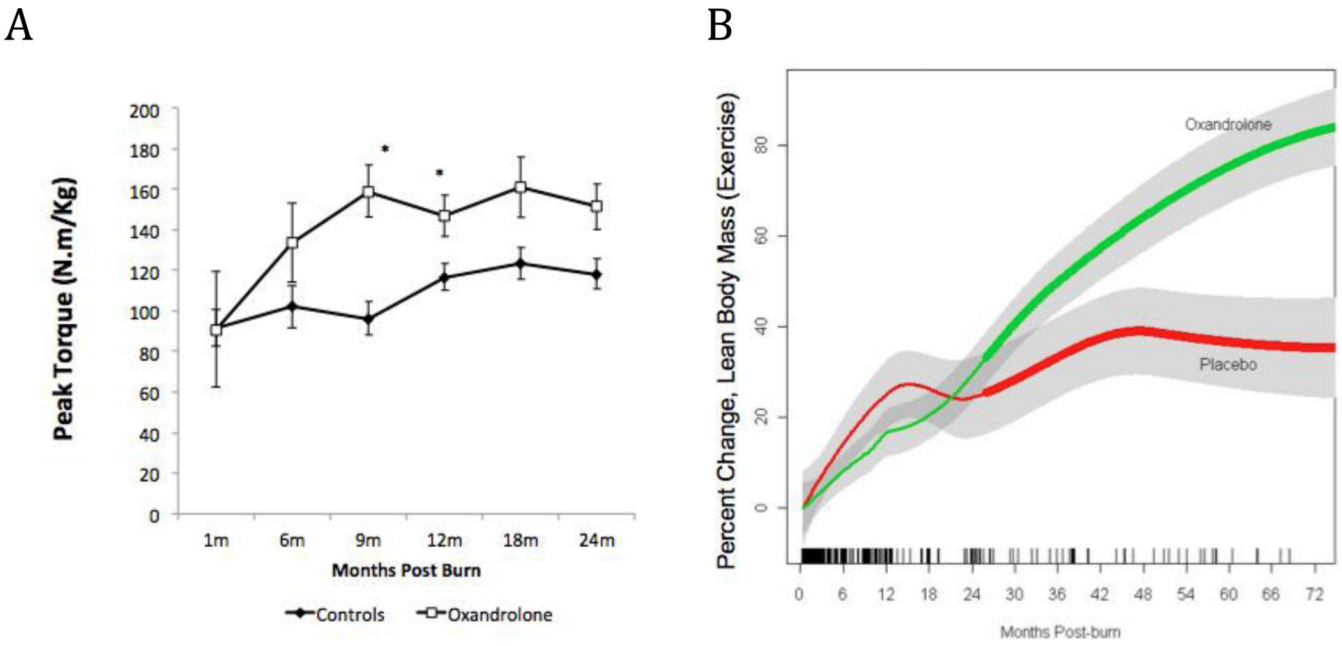

FIGURE 5. Exercise

Combined effect of oxandrolone and exercise on percent change in (A) total lean body mass and (B) muscle strength. In (A), data are represented by the loess-smoothed trend in LBM with shading indicating +/− standard error. Hatch marks across the bottom represent the density of the sampled data at each time point (279 total observations). Time points at which differences are significant are indicated with wider lines ($p<0.05$). In (B), data are expressed as mean ± SEM. *$p<0.05$ vs control.

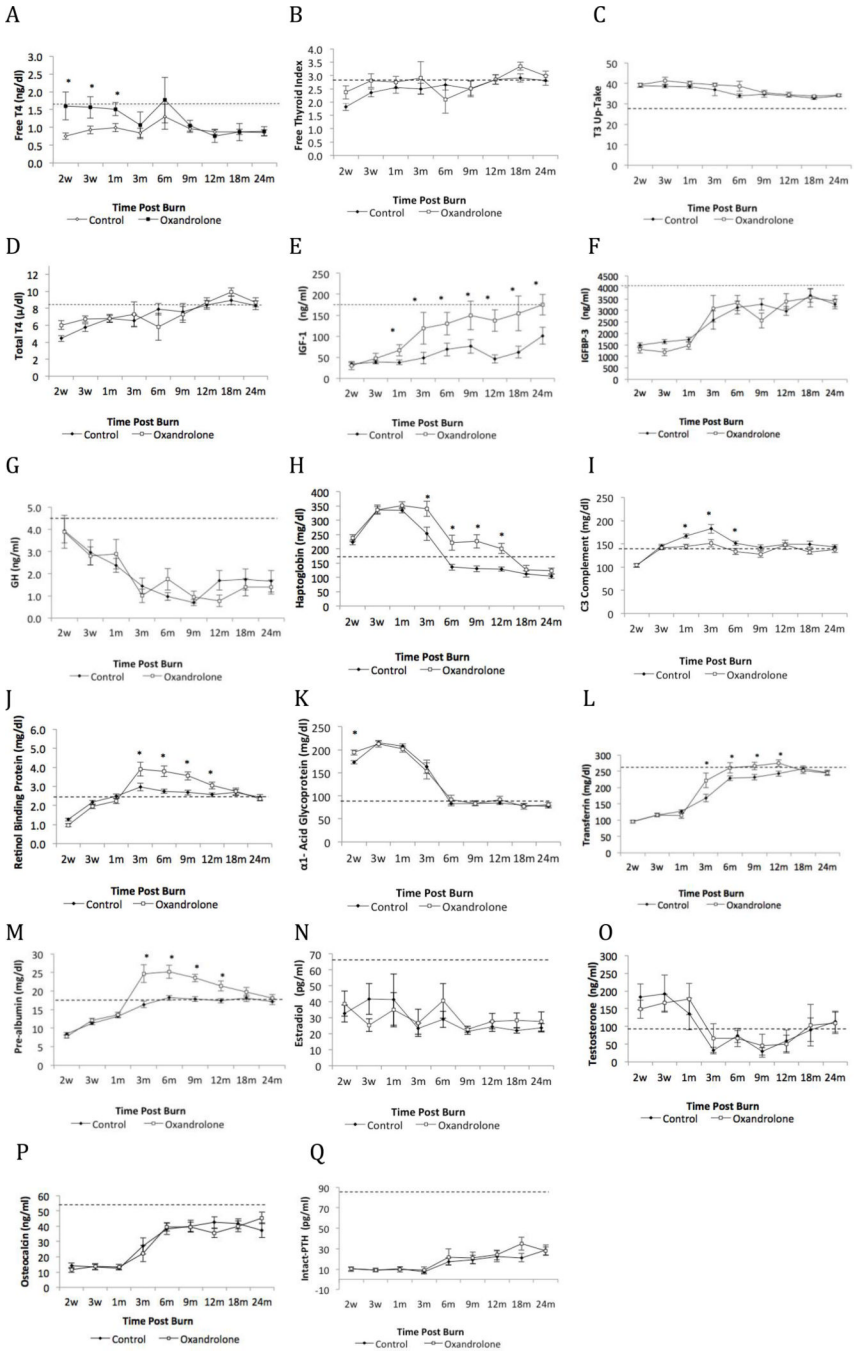

FIGURE 6.

Effect of oxandrolone on serum levels of (A) free T4, (B) free thyroid index, (C) T3 uptake, (D) total T4, (E) IGF-1, (F) IGFBP-3, (G) growth hormone, (H) haptoglobin, (I) C3 complement, (J) retinol-binding protein, (K) α1 acid glycoprotein, (L) transferrin, (M) pre-albumin, (N) estradiol, (O) testosterone, (P) osteocalcin, and (Q) intact parathyroid hormone. Data are expressed as mean±SEM. *$p<0.05$ vs control, w: week, m: month.

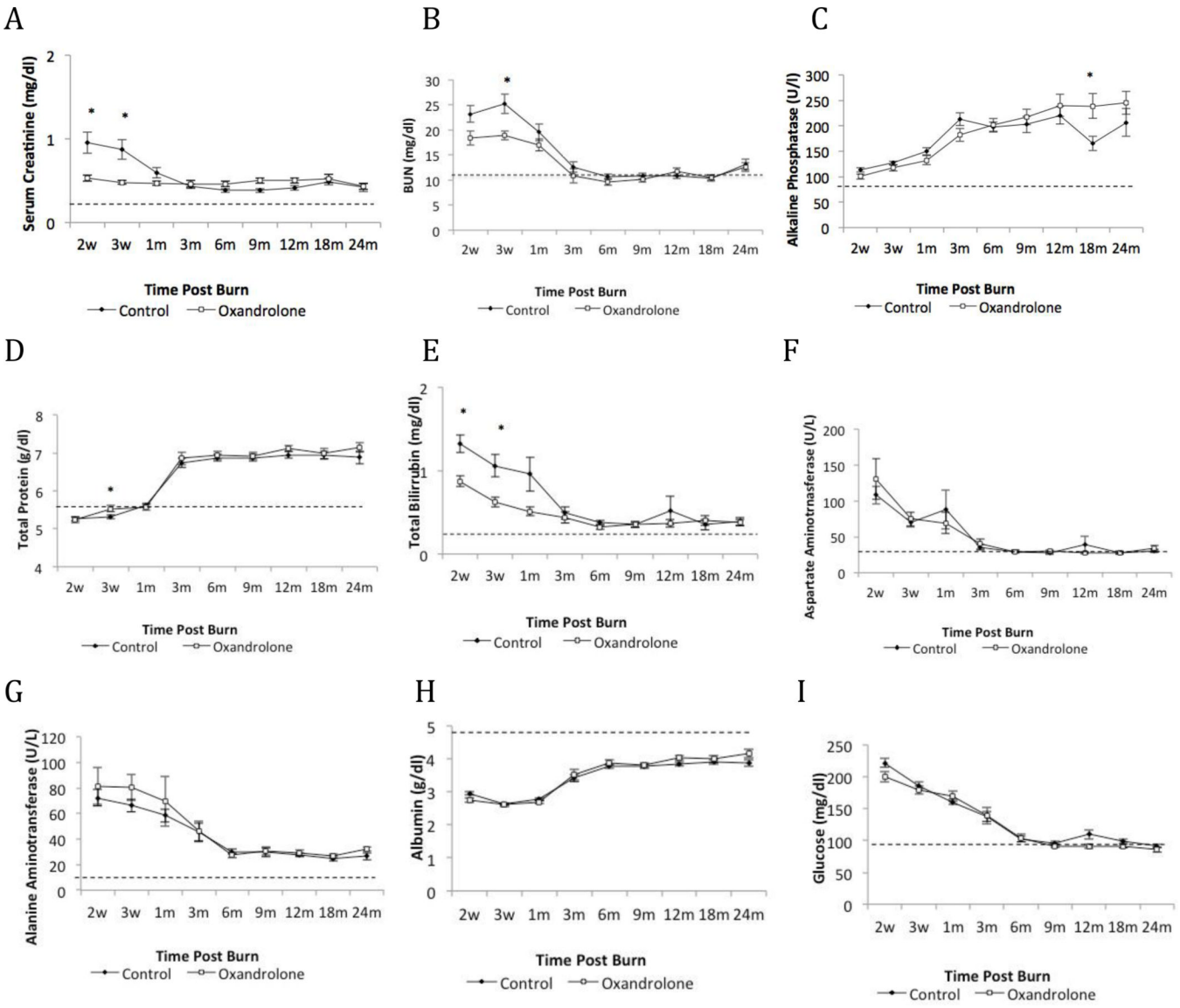

FIGURE 7.

Effect of oxandrolone on levels of (A) serum creatinine, (B) BUN, (C) alkaline phosphatase, (D) total protein, (E) total bilirubin, (F) aspartate aminotransferase, (G) alanine aminotransferase, (H) albumin, and (I) glucose. Data are expressed as mean±SEM. *$p<0.05$ vs control, w: week, m: month.

TABLE 1

Patient Demographics

Variable	Control (n=152)	Oxandrolone (n=70)	p Value
Age, y *	8±5	8±5	0.68
Male, n (%)	99 (65%)	45 (63)	0.80
Hispanics, n (%)	133 (88)	63 (89)	0.52
% TBSA Burned *	57±15	54±15	0.11
Inhalation injury, n (%)	54 (50)	22 (42)	0.33
Length of stay in ICU, d *	30±35	24±16	0.19
Length of stay per % burn *	0.5±0.8	0.4±0.2	0.28
Operations— acute, n *	4.0±2.8	3.6±2.2	0.18
Time between operations, d *	6.6±3.5	6.4±2.4	0.27
Operations— long term, n *	5.9±4.6	4.3±3.3	0.21
Mortality, n (%)	13 (9)	3 (4)	0.24

* Data are expressed as mean ± SEM.

TBSA, total body surface area.

TABLE 2

Growth Distribution at Admission and 1–5 Years Post Burn

Variable	Admission, %	Post burn year, %				
		1	2	3	4	5
>2 SDs below mean height velocity						
Control	20	48*	32*	18	22	27
Oxandrolone	20	8†	7†	16	15	9
>2 SDs below mean weight velocity						
Control	4	46*	26*	19*	18*	21*
Oxandrolone	7	28*†	25*	21	20	19

*p<0.05 vs. admission.

†p<0.05 vs. control.

TABLE 3

Cardiac and Liver Ultrasound Measurements

Variable	Control (n=152)			Oxandrolone (n=70)		
	Discharge	**1 year**	**2 years**	**Discharge**	**1 year**	**2 years**
CO (L/min)	5.1±0.3	4.9±0.3	4.4±0.3	5.2±0.4	4.0±0.3*	3.9±0.3
% Predicted CO	150.7±7.4	148.1±7.2	128.6±9.2	145.6±14.6	115.5±12.4*	98.3±10.9*
CI (L/min/m^2)	5.6±0.4	8.9±3.0	9.8±4.9	6.0±0.7	4.6±0.5	3.9±0.5
SV (mL/m^2)	38.2±2.5	47.4±3.0	43.7±3.0	40.1±3.1	41.9±4.7	43.3±4.1
% Predicted SV	100.5±5.7	121.2±5.4	108.5±6.9	92.8±10.4	103.7±9.2	87.5±8.7
HR (beats/min)	140.4±2.5	111.3±3.6	109.5±5.1	133.6±3.9	105.2±5.5	94.8±4.7*
% Predicted HR	155.8±3.7	123.1±3.4	121.2±4.8	155.1±5.0	110.1±4.4†	109.5±4.3*
Liver size (cm)	12.2±0.4	11.6±0.4	11.4±0.4	12.6±0.4	11.5±0.6	12.4±0.5
Liver weight (g)	3346.8±292.3	3018.5±329.1	2432.2±302.1	3457.9±329.5	2899.2±481.2	3311.8±416.8

Data are expressed as mean±SEM.

*p<0.05 vs control.

HR, heart rate; SV, stroke volume; CI, cardiac Index; CO, cardiac output.

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