

# The Long-Term Effect of Oxandrolone on Hepatic Acute Phase Proteins in Severely Burned Children

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**Background:** Acute phase protein production is a hallmark of severe burns. We wondered whether anabolic treatment with oxandrolone would affect these proteins.

**Methods:** Thirty-five children with  $\geq 40\%$  total body surface area burns were randomized to receive either placebo or oxandrolone (0.1 mg/kg by mouth twice daily) from postoperative day 5 to 1 year postburn. Levels of constitutive proteins and acute phase proteins were measured at admission; at discharge; and at 6, 9,

and 12 months after burn. Total albumin supplementation and hepatic transaminases were also assessed.

**Results:** Constitutive proteins such as albumin, prealbumin, and retinol-binding protein levels increased ( $p < 0.05$ ), and acute phase proteins such as  $\alpha_1$ -acid glycoprotein, C3 complement,  $\alpha_2$ -macroglobulin, and fibrinogen levels significantly decreased in the oxandrolone group compared with placebo ( $p < 0.05$ ). Albumin supplementation during the acute hospitalization was reduced in the oxan-

drolone group. Hepatic transaminases remained within normal levels.

**Conclusion:** Treatment with oxandrolone in severe burns significantly increases constitutive protein and reduces acute phase protein levels.

**Key Words:** Oxandrolone, Constitutive proteins, Acute phase proteins, Severe burns, Albumin, Prealbumin, Retinol-binding protein, Transferrin,  $\alpha_1$ -Acid glycoprotein,  $\alpha_2$ -Macroglobulin, Haptoglobin, C-reactive protein, C3 complement, Hypermetabolism.

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The acute phase response is an orchestrated cascade of events in response to tissue injury, infection, or inflammation. This response leads to reprioritization of liver protein production, with an increase in acute phase proteins and a concomitant decrease in constitutive proteins (Table 1).<sup>1</sup> Constitutive proteins have a wide variety of physiologic functions, and their down-regulation may be potentially harmful for the host. In fact, levels of these proteins have been used to predict mortality in severely ill patients and as clinical markers for patient nutritional status and stress severity and prognostic indicators of improved recovery.<sup>2–4</sup>

Various therapeutic interventions to ameliorate burn-associated complications have been developed. Early excision of the burn eschar removes necrotic tissue, preventing further inflammatory stimulation. This significantly reduces the length of hospital stay, incidence of sepsis, and blood loss associated with delayed excision and skin grafting.<sup>5,6</sup> However, even with these improvements, survivors of severe

burns remain hypermetabolic<sup>7</sup> for a prolonged period of time, with adverse clinical consequences.<sup>8</sup> Historically, clinicians addressed this with caloric supplementation to maintain body weight<sup>9</sup> and hepatic constitutive protein levels.<sup>2</sup> Although weight loss can be diminished in severe catabolic states through nutritional support, nutritional supplementation alone does not abrogate wasting of the peripheral musculature in severely burned patients.<sup>10</sup>

As a result, clinical trials were developed to manipulate the hormonal milieu to prevent catabolism and induce anabolic preservation of protein mass. These agents included growth hormone, insulin, insulin-like growth factor-1 (not presently available), oxandrolone, and testosterone. Growth hormone has been shown to enhance immune function;<sup>11</sup> accelerate wound healing;<sup>12</sup> diminish the hypermetabolic response after major surgery, trauma, sepsis, or thermal injury;<sup>13–15</sup> increase constitutive protein levels; and reduce acute phase proteins.<sup>16</sup> Major shortcomings associated with the use of growth hormone are the requirement for parenteral administration, the high cost of the drug, and the increased risk for hyperglycemia and lipolysis.<sup>12,17</sup> Insulin, an inexpensive anabolic agent, has been used in burn patients to diminish catabolism.<sup>18</sup> However, education and regular follow-up are needed to avoid potential hypoglycemic effects.

Oxandrolone, an oral synthetic analog of testosterone, has been administered to burn patients during their acute hospitalization and long-term treatment to attenuate muscle wasting and improve net protein balance.<sup>19,20</sup> Oxandrolone has also been used successfully in other debilitating diseases such as chronic alcoholic hepatitis, acquired immunodeficiency syndrome, and Turner syndrome to prevent constitu-

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**Table 1** Acute Phase and Constitutive Proteins

Acute Phase Proteins		Constitutive Proteins
Type I	Type II	
$\alpha_1$ -Acid glycoprotein	$\alpha_2$ -Macroglobulin	Albumin
C-reactive protein	$\alpha_1$ -Antitrypsin	Prealbumin
C3 complement	Haptoglobin	Retinol-binding protein
	Fibrinogen	Transferrin

tional growth delays resulting in short stature.<sup>21–23</sup> Oxandrolone has less virilizing potential than other androgenic hormone such as testosterone.<sup>24</sup>

The purpose of our study was to determine the effects of oxandrolone on hepatic acute phase proteins in severely burned children during acute hospitalization and long-term follow-up. We hypothesize that daily administration of oxandrolone will reduce levels of acute phase proteins and increase constitutive protein production when given to severely burned children shortly after acute injury and continued for 1 year into convalescence.

During this study, we specifically studied children who were admitted to our burn center within 7 days of injury. Patients treated elsewhere for a period resulting in a delay in arrival at our hospital, and consequently sustaining greater derangement, were excluded from this study.

## PATIENTS AND METHODS

Severely burned children were enrolled in a 1-year clinical trial investigating the effect of oxandrolone on hepatic acute phase proteins. Inclusion criteria included total body surface area (TBSA) burned  $\geq 40\%$ , age less than 18 years at time of burn, and admission to Shriners Hospitals for Children (Galveston, TX) within 7 days of injury for treatment.

Pregnancy and untreated malignancy were exclusion criteria that precluded enrollment in the study. All patients received standard medical care and burn care treatment including early burn wound excision and skin grafting within 48 hours of admission. Sequential staged excision and grafting were performed until the wounds healed.

Each patient received Vivonex TEN enteral nutrition by nasoduodenal tube. Vivonex is composed of 82% carbohydrate, 15% protein, and 3% fat. Daily caloric intake was given at a rate calculated to deliver 1,500 kcal/m<sup>2</sup> TBSA burned plus 1,500 kcal/m<sup>2</sup> TBSA. This feeding regimen was initiated at admission and continued at a constant rate until the wounds were healed. While outpatients, all subjects were interviewed regarding intake at intervals during convalescence, and no qualitative differences were found. Parenteral albumin was given to maintain serum levels  $>2.5$  g/dL. After resting for 5 days after excision and grafting, patients were walked daily until the next excision and grafting. Patients were treated identically with regard to mobilization and rehabilitation in both study groups throughout the study.

Informed written consent approved by the Institutional Review Board of The University of Texas Medical Branch

was obtained from a legal guardian before enrollment in the study. After obtaining consent, the children were prospectively randomized into two groups. One group received oxandrolone (BTG Pharmaceuticals, Iselin, NJ) 0.1 mg/kg twice daily by mouth, and the other group received placebo starting on postoperative day 5 for 1 full year postinjury. In the event that the patient was unable to tolerate oral ingestion, it was crushed and suspended in 2 mL of ethanol. This suspension was then injected into the nasoduodenal tube and flushed with 20 mL of water.

The hospital pharmacist performed randomization and initiation of pharmacotherapy. Patients and clinicians were blinded to the therapy. Compliance testing was assessed by asking the patients to mark the days on the calendar during which they took the drug. Adverse effects such as clitoromegaly, breast tenderness, hirsutism, and hepatitis were examined at regular intervals by a pediatric endocrinologist.

## Albumin Requirements

Serum albumin concentrations were measured daily. Patients with albumin concentrations less than 2.5 g/dL received 6.25 g/d exogenous albumin for children younger than 2 years of age, 12.5 g/d for children 2 to 9 years old, and 25 g/d for children 10 to 18 years old. Total albumin required each day during acute hospitalization was recorded for each patient within the randomized study groups. Total albumin infused and grams of albumin infused per square meter of burn were compared. Percentages of caloric goals were also compared.

Children returned to Shriners Hospitals for Children-Galveston for evaluation at 3-month intervals after discharge for 1 year. Activity for subjects in both groups was similar in that routine rehabilitation prescriptions were given including home therapy referrals when clinically indicated regardless of group assignment. Serologic assessments of hepatic protein variables were performed during these visits. Five cubic centimeters of whole blood was withdrawn from an indwelling central venous line for determination of nutritional variables and hepatic phase proteins. Prealbumin, transferrin, retinol binding protein,  $\alpha_1$ -acid glycoprotein, C-reactive protein, C3 complement, fibrinogen,  $\alpha_2$ -macroglobulin, and haptoglobin were determined using a Behring Nephelometer-100 (Behring, Deerfield, IL). Albumin was measured from a 12/60 acute phase protein panel using a colorimetric method (630 nm) with dry chemistry detected on a reflectance spectrophotometer (Vitros-250, Johnson & Johnson).

## Statistical Analysis

The effects of treatment and time were analyzed using two-way repeated measures analysis of variance followed by Tukey's test when appropriate. Data were expressed as means  $\pm$  SEM. Statistical significance was accepted at  $p < 0.05$ .

## RESULTS

Thirty-five burned children were initially enrolled in the study. Children who could not return at the requisite time

**Table 2** Demographics

	Control	Oxandrolone
No.	11	10
TBSA (%)	60 ± 4	62 ± 5
Third degree (%)	46 ± 6	51 ± 7
Age (yr)	7 ± 2	9 ± 1
Gender	M 9/F 2	M 8/F 2
Type of burn	Flame, 9 Scald, 2	Flame, 9 Electrical, 1
Smoke inhalation (n)	4	5
Albumin/BSAB (g/m <sup>2</sup> )	586 ± 101	345 ± 49*

BSAB, body surface area burned.

\* Data presented as mean + SEM. Significance accepted at  $p < 0.05$ . Albumin requirement was significantly higher in the control group compared to the oxandrolone group.

points for various reasons (e.g., travel restraints, domiciliary or school circumstances) were excluded. Twenty-one children completed the study at all time points. Demographics are shown in Table 2. The age and burn size were similar in both groups. Children ranged in age from 16 months to 17 years for control subjects and 14 months to 16 years in the oxandrolone-treated group. One child each in both groups fell within the juvenile growth spurt, and one boy in the control group and two boys in the oxandrolone group fell within the adolescent growth spurt. No girls fell in the adolescent growth spurt.<sup>25</sup> The total body surface area burned ranged from 40% to 82% and third-degree burn ranged from 10% to 78% in the controls. In the case of the oxandrolone-treated group, TBSA burned varied from 40% to 90% and third-degree burn varied from 7% to 80%. The control and oxandrolone groups arrived at the hospital at an average of 3 and 3.7 days, respectively. Four children in the control group and five in the oxandrolone group sustained smoke inhalation injury. There were no statistical differences between the groups for any of the given variables.

### Albumin Requirements

Despite equal amounts of caloric intake (1,500 kcal/m<sup>2</sup> body surface area plus 1,500 kcal/m<sup>2</sup> body surface area burned), the amount of albumin supplementation required to maintain serum albumin levels of 2.5 g/dL, expressed as albumin per square meter body surface area burned, was reduced significantly ( $p < 0.05$ ) in patients receiving oxandrolone compared with those receiving placebo during their acute hospitalization (Table 2).

### Constitutive Proteins

Serum albumin concentration was significantly ( $p < 0.05$ ) higher in the oxandrolone group at discharge and at 6 months. In addition, prealbumin was also increased at all time points compared with admission in both groups, with a significant increase ( $p < 0.05$ ) in the oxandrolone group at 6 months after burn compared with the placebo group. Transferrin was decreased in both groups at admission, and trans-

ferrin levels increased slowly but steadily over time in both groups. The levels of retinol-binding protein increased with oxandrolone treatment compared with placebo, with a significant improvement ( $p < 0.05$ ) apparent by 6 months after burn (Table 3).

$\alpha_1$ -Acid glycoprotein concentration increased markedly in untreated subjects during their hospital stay and fell within normal levels by 6 months after burn. Oxandrolone treatment prevents this increase during acute hospitalization, with  $\alpha_1$ -acid glycoprotein levels returning to normal parameters by discharge in comparison with controls ( $p < 0.05$ ). Both groups were within normal levels at 6 months after burn and thereafter. C-reactive protein levels were elevated threefold in both groups at admission and were still moderately elevated at discharge. C-reactive protein levels fell more rapidly toward normal in oxandrolone-treated subjects than in control subjects, although this was not statistically different between the groups. C-reactive protein reached very low levels in oxandrolone-treated patients at 6 months, although control patients had higher levels within the normal range. C-reactive protein remained at very low levels in both groups at 9 months and beyond (Table 3).

A twofold increase in C3 complement from normal levels at admission was noted at discharge in untreated patients. This increase was very minimal in subjects treated with oxandrolone during their hospital course ( $p < 0.05$ ). Levels did not fall to the normal range and remained elevated in both groups for 12 months after burn (Table 3).

Haptoglobin levels increased in both groups during acute hospitalization, with the control group showing a twofold elevation from admission, with a statistically significant difference within the group ( $p < 0.05$ ). No significant changes were seen between the groups (Table 3). In the oxandrolone-treated group, fibrinogen levels remained less than in the control group at all time points, which was statistically different at 6 months after burn ( $p < 0.05$ ).

$\alpha_2$ -Macroglobulin was diminished below normal in both groups at admission and barely achieved low normal levels by discharge. Levels continued to improve with time, and each group showed a statistically significant ( $p < 0.05$ ) increase in levels at all time points compared with admission. The oxandrolone-treated group showed a significant decrease ( $p < 0.05$ ) at 9 months compared with the placebo-treated group (Table 3).

### Clinical Factors

One child developed apparent clitoromegaly 6 months after injury. The child had sustained a perineal burn and, although edema was thought to be a significant contributing factor, the drug was discontinued and the condition resolved. It is unclear whether this in fact was true clitoromegaly attributable to a virilizing side effect of the drug or the resolution of postburn edema. No other patients developed hirsutism, acne, hepatitis (Table 4), clitoromegaly, or behavioral changes. No deaths occurred in either group. One patient

**Table 3** Constitutive Proteins and Acute Phase Proteins

	Admission		Discharge		6 Mo		9 Mo		12 Mo	
	Control	Oxandrolone	Control	Oxandrolone	Control	Oxandrolone	Control	Oxandrolone	Control	Oxandrolone
Constitutive proteins										
Albumin (3–5.5 g/dL)	3.2 ± 0.2	3 ± 0.1	2.2 ± 0.1 <sup>†</sup>	3.2 ± 0.2*	3.3 ± 0.2	3.8 ± 0.1 <sup>†</sup>	3.8 ± 0.2 <sup>†</sup>	4 ± 0.1 <sup>†</sup>	3.8 ± 0.1 <sup>†</sup>	4 ± 0.2 <sup>†</sup>
Prealbumin (25–45 mg/dL)	6.4 ± 0.5	7 ± 0.4	13.8 ± 1.3 <sup>†</sup>	16.9 ± 1.5 <sup>†</sup>	15.1 ± 1.4 <sup>†</sup>	25 ± 1.3 <sup>†*</sup>	20.4 ± 2.3 <sup>†</sup>	25.1 ± 1.6 <sup>†</sup>	21.5 ± 1.2 <sup>†</sup>	24.5 ± 2.6 <sup>†</sup>
Retinol-binding protein (3–6 mg/dL)	1.2 ± 0.1	1.2 ± 0.1	2.4 ± 0.3 <sup>†</sup>	2.5 ± 0.2 <sup>†</sup>	2.7 ± 0.4 <sup>†</sup>	4 ± 0.4 <sup>†</sup>	2.7 ± 0.5 <sup>†</sup>	3.7 ± 0.3 <sup>†</sup>	2.8 ± 0.1	3.5 ± 0.2 <sup>†</sup>
Transferrin (220–420 mg/dL)	93 ± 7	90 ± 7	158 ± 14	131 ± 13	197 ± 23 <sup>†</sup>	216 ± 26 <sup>†</sup>	224 ± 15 <sup>†</sup>	245 ± 35 <sup>†</sup>	251 ± 17 <sup>†</sup>	258 ± 29 <sup>†</sup>
Type I acute phase protein										
α <sub>1</sub> -acid glycoprotein (55–140 mg/dL)	170 ± 17	190 ± 15	229 ± 22 <sup>†</sup>	141 ± 19*	91 ± 16 <sup>†</sup>	96 ± 16 <sup>†</sup>	85 ± 11 <sup>†</sup>	86 ± 12 <sup>†</sup>	83 ± 11 <sup>†</sup>	100 ± 4 <sup>†</sup>
C-reactive protein (0–5 mg/dL)	14 ± 3	14 ± 2	8 ± 2	6 ± 2 <sup>†</sup>	3 ± 2 <sup>†</sup>	1 ± 0 <sup>†</sup>	1 ± 0 <sup>†</sup>	0.5 ± 0 <sup>†</sup>	1 ± 0 <sup>†</sup>	1 ± 0 <sup>†</sup>
C3 complement (50–90 mg/dL)	79 ± 5	98 ± 8	178 ± 13 <sup>†</sup>	131 ± 10* <sup>†</sup>	126 ± 10 <sup>†</sup>	108 ± 6	124 ± 7 <sup>†</sup>	109 ± 8	119 ± 6 <sup>†</sup>	122 ± 9
Type II acute phase protein										
α <sub>2</sub> -Macroglobulin (150–420 mg/dL)	113 ± 10	111 ± 9	163 ± 13	172 ± 23	266 ± 31 <sup>†</sup>	255 ± 17 <sup>†</sup>	339 ± 27 <sup>†</sup>	244 ± 16* <sup>†</sup>	312 ± 22 <sup>†</sup>	261 ± 26 <sup>†</sup>
Fibrinogen (150–375 mg/dL)	430 ± 65	518 ± 50	617 ± 36 <sup>†</sup>	520 ± 33	538 ± 59	335 ± 32* <sup>†</sup>	373 ± 32	341 ± 37 <sup>†</sup>	361 ± 26	336 ± 50
Haptoglobin (50–220 mg/dL)	201 ± 30	269 ± 22	412 ± 32 <sup>†</sup>	321 ± 28	133 ± 21	189 ± 25	145 ± 18	206 ± 47	122 ± 23	194 ± 38

Data presented as mean ± SEM.

\* Significantly different from the control group at the same time point ( $p < 0.05$ ).

† Significantly different from admission within group ( $p < 0.05$ ).

**Table 4** Liver Enzymes

	Normal Levels	Admission		6 Mo		9 Mo		12 Mo	
		Control	Oxandrolone	Control	Oxandrolone	Control	Oxandrolone	Control	Oxandrolone
Alanine amino transaminase (IU/L)	5–35	26 ± 3	40 ± 6	21 ± 2	36 ± 5	20 ± 2	22 ± 2	37 ± 2	26 ± 3
Alkaline phosphatase (IU/L)	35–125	129 ± 11	125 ± 8	112 ± 17	124 ± 15	125 ± 16	214 ± 20	137 ± 21	125 ± 25
Gamma glutamyl transaminase (IU/L)	7–66	82 ± 14	74 ± 13	19 ± 4	21 ± 3	20 ± 3	21 ± 4	22 ± 1	20 ± 4
Total bilirubin (mg/dL)	0.1–1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1

in the oxandrolone group developed septicemia during his hospital course. The patient arrived from a local hospital in Mexico on postburn day 7. The patient was critically ill on arrival, with hyperthermia, hypoxemia, hemodynamic derangement, and clinical signs consistent with systemic sepsis. *Pseudomonas aeruginosa* was isolated from tracheal aspirates and blood cultures. Sepsis improved after immediate total excision of his burn wound followed by a 10-day course of parenteral antibiotics. An average of  $7 \pm 0.5$  and  $8 \pm 0.6$  operations were performed for the control and oxandrolone groups, respectively, from admission to 1 year after burn. No differences between the groups were found.

## DISCUSSION

Severe burn lead to a hypermetabolic state<sup>7</sup> in which overall protein breakdown exceeds protein synthesis, endangering the well-being of the severely burned patient.<sup>22</sup> Various hormonal derangements also lead to a shift in hepatic protein production. In this prospective placebo-controlled study, we sought to determine the effect of oxandrolone on hepatic acute phase serum levels. We found that treatment with oxandrolone has a profound effect on many of the hepatic protein levels.

Albumin is the most abundant protein maintaining plasma oncotic pressure, which falls dramatically in severe injury. Our study showed that administration of oxandrolone acutely to severely burned children significantly improved albumin values, increasing them to normal levels during their acute hospitalization and also for 6 months postburn compared with the placebo group. This is corroborated by reduction in the perceived need for albumin supplementation in the oxandrolone-treated group. The serum albumin level continued to increase in both groups after discharge, with the control group reaching their normal levels at 6 months. The value of albumin in the oxandrolone group is better maintained with respect to the control group throughout the treatment period.

In the control group, prealbumin did not reach normal levels even 1 year removed from injury, whereas in the oxandrolone-treated group, the prealbumin value increased steadily, with a significant increase compared with the placebo group at 6 months. This increase coincides with the

increase in the level of albumin seen with oxandrolone treatment. We conclude that oxandrolone has a profound effect on the levels of albumin and prealbumin. It remains to be determined whether this is a stimulated increase in hepatic production or a diminished disposal.

The iron-binding protein transferrin increases in both groups for 1 year postburn. All time points are statistically significant from admission within the groups. Transferrin reaches its normal level at 9 months postburn in both groups. Oxandrolone treatment did not produce any significant effect.

Retinol-binding protein, the carrier of vitamin A, increased in both groups after admission. It is commonly used as a marker for nutritional capacity in the liver and responds rapidly to dietary intervention.<sup>26</sup> The values of the oxandrolone-treated group are well above the values of the control group at all time points after discharge, with a statistically significant difference at 6 months after burn. Although the oxandrolone-treated group reached the normal level at 6 months postburn, the control group continued to be below the normal levels at 1 year postinjury. This showed that hepatic protein regulation had not regained normal function even at 1 year into convalescence. Retinol-binding protein has a binding site for one molecule of retinol and circulates in the plasma together with prealbumin in the form of a protein complex in a molar ratio of 1:1. Therefore, a reduction in one will always reflect in the other. This binding to prealbumin prevents greater glomerular loss of the retinol-binding protein, and the oxandrolone-stimulated increase in prealbumin levels may therefore be partly responsible for increases in retinol-binding protein levels. Because of the short half-life of retinol-binding protein (11 hours), it is an excellent indicator of early malnutrition (half-lives: albumin, 21 days; prealbumin, 2 days).<sup>27</sup>

$\alpha_1$ -Acid glycoprotein, the major type I acute phase protein, was above normal levels at admission. In the control group,  $\alpha_1$ -acid glycoprotein increased during acute hospitalization and returned to normal levels at 6 months postburn, whereas in the oxandrolone-treated patients, the values decreased significantly compared with the control group during acute hospitalization and reached normal levels at discharge.

C-reactive protein was originally named for its ability to bind with the C-polysaccharide of *Pneumococcus*. It acts as

an opsonin for bacteria, parasites, and immune complexes and can activate the classic complement pathway. C-reactive protein can increase severalfold, depending on the disease and its severity. C-reactive protein begins well above the normal levels at admission but continues to decrease in both groups, reaching normal levels by 6 months postburn. Oxandrolone treatment has no effect on these changes.

C3 complement, which is a marker for intrinsic and extrinsic pathway function, continued to be above normal levels for more than 1 year postinjury in both groups. Although we found a significant decrease at discharge in the oxandrolone-treated group, the values in both groups were above normal levels. This shows that there is ongoing inflammation in severely burned children for more than 1 year postburn. This is consistent with a prolongation of the hypermetabolic state seen in severely burned children.<sup>7</sup> C3 complement, therefore, may be the best marker for detecting when the long-term acute phase proteins return to normal levels in severely burned children.

Haptoglobin returned to normal levels at 6 months postburn in both groups. The increase in haptoglobin levels during acute hospitalization was attenuated with oxandrolone treatment. Fibrinogen, which is converted to fibrin in the formation of blood clot, returned to normal range within the first 6 months after injury, with a significant difference in the oxandrolone-treated group. Although all the other acute phase proteins decreased in the first 6 months,  $\alpha_2$ -macroglobulin, a binding protein for many cytokines and growth factors, increased after discharge for up to 9 months postburn in both groups. The oxandrolone-treated group showed a significant decrease at 9 months postburn compared with the placebo-treated group. Thereafter, the value declined in both groups. This is the only acute phase protein of type I and type II that showed an increase during the postburn period. It may be because of the unique function of  $\alpha_2$ -macroglobulin as a proteinase inhibitor serving as a common scavenger of proteinases, thereby protecting the blood and tissue proteins against degradation. The increase in  $\alpha_2$ -macroglobulin levels makes it unique among the acute phase proteins. In type II acute phase proteins, oxandrolone has a significant effect on fibrinogen and  $\alpha_2$ -macroglobulin.

In summary, oxandrolone increases constitutive proteins such as albumin, prealbumin, and retinol-binding protein compared with placebo, where prealbumin and retinol-binding protein continue to be below normal values at 1 year postburn. Type I and type II acute phase proteins returned to their normal levels by 6 months postburn in both groups, except for C3 complement, which continued to be elevated for at least 1 year postinjury. Six months is an important time point for most of the hepatic phase proteins to return to their normal levels. This shows that the liver has partially but not fully restored function even after 1 year of convalescence, and that oxandrolone plays a significant role in increasing constitutive proteins while diminishing acute phase proteins. Lack of effects after 6 months may reflect diminishing effec-

tiveness of oxandrolone because of tachyphylaxis to the compound through inhibitory factors or the effects of the drug are maximized to the extent that no further stimulation through its pathways are possible. Study of the acute phase proteins shows that even though external injuries are healed, normal homeostasis takes more than 1 year for full recovery. Further follow-up of burned children is needed to precisely determine the time point at which normal hepatic synthetic function is regained.

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## DISCUSSION

**Dr. Basil A. Pruitt, Jr.** (San Antonio, Texas): This and previous studies from Dr. Herndon's burn center have expanded our understanding of the metabolic response to injury and identified interventions that can beneficially modify postinjury catabolism. In this article, the authors report that oxandrolone significantly increases constitutive protein levels and reduces acute phase protein levels. There are several concerns that must be addressed to help us evaluate their conclusions.

You state that caloric intake remained constant throughout the study period. Since weight presumably increased across time, how was constancy of caloric intake monitored and documented? Was a nutritional diary maintained by each patient? In short, does oxandrolone increase appetite, and could a difference in nutritional intake be responsible, at least in part, for your findings?

You further state that patients were treated identically with regard to mobilization and rehabilitation in both study groups throughout the study. However, you note that for clinically indicted problems, physical and occupational therapy referrals to departments close to the subject's homes were given. Those contradictory statements suggest that differences in activity levels existed and could have affected your results.

In earlier studies, you reported that growth spurts influence metabolic indices in convalescent burn patients. I believe that the frequency, duration, and magnitude of growth spurts vary with age. You note that age in the two groups was similar but ranged from 16 months to 17 years in the control group and from 14 months to 16 years in the treatment group. In light of those broad age spans, we need to know whether the distribution of ages was different in the two age groups, since that could influence the occurrence and characteristics of growth spurts within each group and influence outcome independent of oxandrolone.

One other variable that could affect the outcomes you studied is reconstructive surgery interventions during the study period. We need to know whether differences in the timing, magnitude, and number of operations could have influenced your findings.

Some of the protein assays are puzzling and seem to be of tenuous clinical importance. What does a C-reactive protein of zero in the oxandrolone group at 9 months, bracketed at 6 and 12 months by values of 1, really mean? It seems paradoxical that haptoglobin levels are higher at 6, 9, and 12 months in the oxandrolone group. How do you interpret that? Could that be a type II error because you have a small number of patients in both groups? In that same vein, how do you explain a higher transferrin level at discharge in the control group? The differences in albumin levels seem modest at best. Is there any clinical impact of an 0.5-, 0.2-, and 0.2-mg/dL higher level of albumin in the oxandrolone-treated patients at 6, 9, and 12 months, respectively?

You credit the better-maintained albumin levels in the oxandrolone group with normalizing compartment fluid distribution and limiting unnecessary postoperative edema. To confirm that claim, do you have measurements of blood volume, extracellular fluid volume, and total body water or, alternatively, wet-weight/dry-weight ratios of selected tissues.

Finally, it is most encouraging to know that in addition to its salutary effects on lean body mass, oxandrolone may ameliorate the postinjury reprogramming of hepatic protein synthesis priorities to enhance constitutive protein production and reduce acute phase protein production. In light of your earlier studies, can you envision combining oxandrolone with another anticatabolic agent, perhaps propranolol, to obtain synergistic effects?

**Dr. Nabil Atweh** (Bridgeport, Connecticut): I'd like to congratulate, also, the presenters on these data, and it simulates very much our experience with the other population. One question I have for them is, was there any difference between girl and boy responders and was the muscularizing effect detected in any of this population? Thank you very much.

**Dr. Suchmor Thomas** (closing): Dr. Pruitt, one of your first questions was about the dietary intake of these children. These children actually kept a diary for us to be analyzed up to their acute hospitalization. After their acute hospitalization,

as you said, it's right, because we basically don't know about the dietary intake of these children.

Then, about the early walking, whether there was any significant difference in these children in walking or in exercise. The number we had was—we had only 11 children in the oxandrolone group and 10 in the control group—so basically the number was less. There were only four exercises per group, and exercises were started from 6 to 9 months, so most of the hepatic acute phase proteins returned to normal level by 6 months; when there are more than 20 or 25 patients, we can significantly answer that question.

Another question was about the growth spurt seen at this age. It is absolutely right that the age range was different. There was a broad age range, from 6 months to 17 years, but the age range was similar in both groups.

The other question was about C-reactive protein. The C-reactive protein values can actually go up to 1,000 times higher. Most of the time, it's very difficult to analyze C-reactive protein, so most clinicians only look into the C-reactive proteins during the patient's acute hospitalization. After that, it's almost zero or negligible.

The other question is about the reconstructive surgery. We have actually not looked into those data yet, but that's a very good suggestion, and we are looking into the effects of oxandrolone on scar formation and the effects on reducing the operations.

Another question was about the higher levels of haptoglobin. Most of the hepatic acute phase proteins increase about 5- to 10-fold within the first 24 hours of burn. That may be why our time of admission was 3 days in the control group and in 3.7 days in the oxandrolone-treated group was; that may be the preliminary reason.

Another question was whether we measured the blood volume, extracellular fluid, or total body water. No, we have not done that, but I think we should have done so to determine the effects of albumin.

What is the clinical relevance of increase in the C3 complement? The C3 complement findings may be right because, in this study, we have seen that it's not returning to normal levels, even at 1 year both in the oxandrolone-treated group and in the control group.

It may be because of the progressive edema and itching associated with the hypertrophic scar. Finally, there was a question about what the effect was of this on the lean body mass and on the bone mineral content. This was a study lasting 1 year. Actually, these are preliminary data only, so these are the changes we have seen for lean body mass.

We have seen no statistically significant difference, even though there was an increase in the oxandrolone-treated group. From the power analysis, we have seen that the number of patients should be 22 to give a statistically significant difference.