

EXERCISE-INDUCED HORMONE ELEVATIONS ARE RELATED TO MUSCLE GROWTH

GERALD T. MANGINE,¹ JAY R. HOFFMAN,² ADAM M. GONZALEZ,² JEREMY R. TOWNSEND,² ADAM J. WELLS,² ADAM R. JAJTNER,² KYLE S. BEYER,² CARLEIGH H. BOONE,² RAN WANG,² AMELIA A. MIRAMONTI,² MICHAEL B. LAMONICA,² DAVID H. FUKUDA,² E. LEA WITTA,² NICHOLAS A. RATAMESS,³ AND JEFFREY R. STOUT²

¹Department of Exercise Science and Sport Management, Kennesaw State University, Kennesaw, Georgia; ²Department of Educational and Human Sciences, Institute of Exercise Physiology and Wellness, University of Central Florida, Orlando, Florida; and ³Health and Exercise Science, The College of New Jersey, Ewing, New Jersey

ABSTRACT

Mangine, GT, Hoffman, JR, Gonzalez, AM, Townsend, JR, Wells, AJ, Jajtner, AR, Beyer, KS, Boone, CH, Wang, R, Miramonti, AA, LaMonica, MB, Fukuda, DH, Witta, EL, Ratamess, NA, and Stout, JR. Exercise-induced hormone elevations are related to muscle growth. *J Strength Cond Res* 31(1): 45–53, 2017—Partial least squares regression structural equation modeling (PLS-SEM) was used to examine relationships between the endocrine response to resistance exercise and muscle hypertrophy in resistance-trained men. Pretesting (PRE) measures of muscle size (thickness and cross-sectional area) of the vastus lateralis and rectus femoris were collected in 26 resistance-trained men. Participants were randomly selected to complete a high-volume (VOL, $n = 13$, 10–12RM, 1-minute rest) or high-intensity (INT, $n = 13$, 3–5RM, 3-minute rest) resistance training program. Blood samples were collected at baseline, immediately postexercise, 30-minute, and 60-minute postexercise during weeks 1 (week 1) and 8 (week 8) of training. The hormonal responses (testosterone, growth hormone [22 kD], insulin-like growth factor-1, cortisol, and insulin) to each training session were evaluated using area-under-the-curve (AUC) analyses. Relationships between muscle size (PRE), AUC values (week 1 + week 8) for each hormone, and muscle size (POST) were assessed using a consistent PLS-SEM algorithm and tested for statistical significance ($p \leq 0.05$) using a 1,000 samples consistent bootstrapping analysis. Group-wise comparisons for each relationship were assessed through independent t -tests. The model explained 73.4% ($p < 0.001$) of variance in muscle size at POST.

Significant pathways between testosterone and muscle size at PRE ($p = 0.043$) and muscle size at POST ($p = 0.032$) were observed. The ability to explain muscle size at POST improved when the model was analyzed by group (INT: $R^2 = 0.882$; VOL: $R^2 = 0.987$; $p < 0.001$). No group differences in modal quality were found. Exercise-induced testosterone elevations, independent of the training programs used in this study, seem to be related to muscle growth.

KEY WORDS structural equation modeling, partial least squares regression, endocrine response, hypertrophy

INTRODUCTION

The moderately high-intensity and high-volume (8–12 repetition maximum [RM] or more), short-rest interval (1–2 minutes) resistance training model has long been used by individuals striving to increase muscle mass and is thought to be ideal for skeletal muscle hypertrophy (3,26). In part, the scientific support for this hypothesis relied on evidence demonstrating greater postexercise concentrations in anabolic hormones, whose postexercise elevation would potentially improve the likelihood of hormone–receptor binding and initiating a cascade of intracellular reactions that affects muscle growth (2,18,19). However, the validity of this concept is questionable. Hormonal influence is dependent on receptor availability in activated muscle (19), and androgen receptor content has been reported to decline after moderately high-intensity, high-volume (10RM) resistance training (27). Exercise-induced elevations in circulating anabolic hormones (i.e., testosterone and insulin-like growth factor 1 [IGF-1]) have been demonstrated to be comparable between high-volume and high-intensity training protocols (12,21,29). Recent evidence has also shown that increases in muscle hypertrophy may be comparable between these training paradigms and seem to occur without significant elevations (from baseline) in several endocrine measures (i.e., testosterone, growth hormone, cortisol, and IGF-1) (38,39). Several investigators have sug-

Address correspondence to Gerald T. Mangine, gmangine@kennesaw.edu.

31(1)/45–53

Journal of Strength and Conditioning Research
© 2016 National Strength and Conditioning Association

gested that the exercise-induced hormone response may not influence muscle growth (24,37–39). Furthermore, evidence in resistance-trained men does not support the high-volume, short-rest interval model as being more advantageous (in comparison to a high-intensity, longer-rest interval model) for developing muscle strength and hypertrophy (4,21,28). Consequently, evidence demonstrating a clear relationship between postexercise hormone concentrations and muscle hypertrophy is lacking.

Few studies have attempted to relate the postexercise endocrine response to changes in muscle hypertrophy (1,23,35,40). However, the findings of these studies are contradictory and may have been influenced by differences in techniques used to measure relationships between the acute hormonal responses and subsequent muscle hypertrophy. For instance, 2 of these studies used Pearson's product moment correlation coefficients to assess the aforementioned relationships in small sample populations ($n = 8$ – 10) (1,23), which increases the odds of spurious observations (34). Recently, Walker et al. (35) accounted for this limitation by using a nonparametric statistical measure (i.e., Spearman's rank correlation coefficients), but lost contextual information through the statistic's ranking process. Similarly, a significant amount of information is lost when using either of these statistical procedures for assessing the relationships between concepts that exist across time (i.e., hypertrophy, multiple endocrine responses) because the statistics can only assess the relationship between 2 sets of values. To examine the correlation between hypertrophy and the endocrine response, either muscle hypertrophy (1,23,35,40) or the endocrine response (1,23,35) from baseline and posttesting must be transformed into a single value (i.e., change score, average score). Furthermore, the validity of this type of relationship (i.e., correlating one variable to one other) is based on the assumption that the related variables were collected without systematic or random error (6,14). In each of these studies (1,23,35,40), data were collected or analyzed using procedures (e.g., magnetic resonance imaging, dual-energy x-ray absorptiometry, assay analysis, etc.) that were dependent on technician reliability and were therefore subject to error (36). Consequently, previously observed relationships between the endocrine response to resistance training and muscle hypertrophy must be viewed with caution.

An alternative approach to assessing the relationships between the postexercise endocrine response and muscle hypertrophy is to use structural equation modeling. This manner of statistical procedure uses multiple independent and dependent variables to describe latent constructs, whose relationships are then statistically assessed (6,11,14). The statistical assessment can be co-variance or variance-based, though a variance-based procedure does not rely on typical parametric assumptions (e.g., normal distribution, large sample size, etc.). Additionally, the use of multiple indicator

variables (e.g., muscle thickness and cross-sectional area) to describe a single latent variable (e.g., muscle hypertrophy) maximizes their variance and permits systematic and random modeling errors (14). Partial least squares structural equation modeling (PLS-SEM) is a variance-based procedure that uses bootstrapping to statistically assess the relationships between multiple latent variables that are developed from several collected indicator variables (6,14). Previously, PLS-SEM and bootstrapping have been used to assess relationships within the biomedical sciences (5,20,41), but it has not yet been used to assess the relationships between the postexercise endocrine response and muscle hypertrophy. Therefore, the purpose of this investigation was to use PLS-SEM to assess the relationships between muscle hypertrophy and the endocrine responses to resistance exercise across 8 weeks of training in resistance-trained men. Furthermore, we aimed to determine whether any observed relationships remained consistent when using either a high-volume, short-rest interval or a high-intensity, long-rest interval resistance training protocol.

METHODS

Experimental Approach to the Problem

Full details of the experimental protocol and training design are described elsewhere (21). Briefly, participants were required to complete a 2-week preparatory training program before the onset of the actual training program. During this phase, 4 participants removed themselves from the study for reasons unrelated to the investigation. After the preparatory period (week 0), pre-training (PRE) assessments of muscle thickness and cross-sectional area (CSA) were performed at a standardized time of day and before initiating any physical activity. Participants were then randomly assigned to one of the 2 training groups: a high-intensity, low-volume training group (INT; $n = 13$; 24.7 ± 3.7 years; 89.5 ± 15.9 kg; 180.1 ± 5.8 cm) or a high-volume, moderate intensity training group (VOL; $n = 13$; 24.2 ± 2.7 years; 90.1 ± 11.7 kg; 169.5 ± 30.1 cm). During training, participants were required to complete at least 28 resistance training sessions ($\sim 90\%$) of an 8-week resistance-training program (4 sessions per week⁻¹) that included 6 upper- and lower-body exercises during each session, under the direct supervision of certified strength and conditioning specialists. Kilocalorie and macronutrient intake was monitored for changes through 3-day food diaries collected weekly, whereas postexercise nutrition was standardized by providing ~ 235 ml of chocolate milk (170 calories; 2.5 g Fat; 29 g Carbohydrate; 9 g protein) or Lactaid (150 calories; 2.5 g Fat; 24 g Carbohydrate; 8 g protein) to each participant immediately after each workout. Pre-exercise and postexercise blood samples were collected during the first and last weeks of the 8-week training program. Posttesting (POST) occurred during the week 9.

TABLE 1. Individual measures of muscle size before and after 8 weeks of resistance training.

	Rectus femoris				Vastus lateralis			
	Cross-sectional area		Muscle thickness		Cross-sectional area		Muscle thickness	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Volume								
Subject 1	13.6	14.0	2.3	2.6	28.1	30.9	1.6	1.7
Subject 2	13.1	12.3	2.5	2.3	36.0	37.5	1.6	1.6
Subject 3	20.5	19.9	3.2	3.4	40.2	42.1	2.2	2.2
Subject 4	19.9	19.8	2.8	2.8	35.5	42.0	1.4	1.6
Subject 5	16.7	18.1	2.7	2.8	34.2	35.9	1.9	2.1
Subject 6	18.6	17.7	3.2	3.2	37.0	40.1	2.0	2.3
Subject 7	15.3	17.3	2.8	2.6	39.0	35.9	1.9	1.8
Subject 8	15.7	17.1	2.4	2.6	31.6	35.2	1.8	2.0
Subject 9	13.9	14.0	2.3	2.4	45.4	46.8	1.7	1.5
Subject 10	17.4	15.3	2.9	2.8	40.6	39.0	1.9	1.9
Subject 11	16.1	16.4	3.1	2.9	49.3	47.9	2.5	2.4
Subject 12	22.6	22.5	3.9	3.4	54.5	56.8	2.3	2.4
Subject 13	14.2	13.9	2.7	2.6	32.9	31.8	1.6	1.6
Intensity								
Subject 14	8.9	8.8	2.1	2.2	35.6	39.4	2.0	2.1
Subject 15	10.9	11.3	2.5	2.3	29.5	32.2	1.3	1.7
Subject 16	14.2	15.9	2.5	2.6	33.7	37.8	1.4	1.8
Subject 17	17.2	16.7	2.7	2.7	37.1	38.2	2.2	1.8
Subject 18	14.4	14.9	3.0	2.6	40.0	37.7	1.5	1.8
Subject 19	14.9	14.7	2.4	2.3	39.2	40.9	1.7	1.7
Subject 20	16.2	16.7	2.7	2.7	33.3	36.1	1.8	2.3
Subject 21	10.5	10.8	2.3	2.5	38.9	45.7	1.4	1.6
Subject 22	16.7	15.6	2.7	2.5	39.4	42.8	1.8	2.2
Subject 23	16.2	20.9	2.7	3.1	45.3	51.9	1.7	2.0
Subject 24	26.6	26.8	3.5	3.5	48.8	69.3	1.9	1.8
Subject 25	15.3	15.4	2.4	2.4	37.0	36.8	2.0	1.8
Subject 26	10.5	10.4	2.3	2.3	25.3	32.1	1.3	1.4

Subjects

A complete description of the methods, study design, and participant characteristics has been previously reported (21). However, the participant characteristics presented here reflect data collapsed across groups since they were analyzed as a single group for a segment of this investigation. Additionally, the characteristics of each group reflect subsamples of the original groups because 2 participants (one member from each group) chose not to provide blood samples for analysis, and the data set for one other participant (intensity group) was not complete. Briefly, 33 physically-active, resistance-trained men who had been regularly participating (at the time of recruitment) in resistance training for a minimum of 2 years (5.7 ± 2.2) and free of any physical limitations (determined by medical history questionnaire and PAR-Q) were recruited to participate in an 8-week full-body resistance training program. Before participating, all participants were informed of all procedures, risks, and benefits associated with the study and each participant provided his written

informed consent to participate in the study. This investigation was approved by the New England Institutional Review Board. The age range of the participants was 19.3 years to 33.0 years.

Muscle Cross-Sectional Area and Thickness

Noninvasive skeletal muscle ultrasound images were collected from the dominant thigh of each participant using previously described procedures (21) to measure muscle cross-sectional area (CSA; $\pm 0.1 \text{ cm}^2$) and muscle thickness (MT; $\pm 0.1 \text{ cm}$). Briefly, the same investigator identified all anatomical locations of interest using standardized landmarks for the rectus femoris (RF) and vastus lateralis (VL) and collected all images using a 12 MHz linear probe scanning head (General Electric LOGIQ P5; Wauwatosa, WI, USA). For all images, the extended field of view mode (Gain = 50 dB; Image Depth = 5 cm) was used to capture 2 consecutive panoramic images of the muscular regions of interest. After image collection, the ultrasound data were

TABLE 2. Individual area-under-the-curve endocrine responses to exercise at the onset and conclusion of 8-weeks of resistance training.*

	Cortisol		Growth hormone		IGF-1		Insulin		Testosterone	
	Wk 1	Wk 8	Wk 1	Wk 8	Wk 1	Wk 8	Wk 1	Wk 8	Wk 1	Wk 8
Volume										
Subject 1	2362	2449	24.3	28.5	454	442	276	296	38.1	34.7
Subject 2	1326	1144	15.7	6.5	488	497	297	315	24.3	25.6
Subject 3	2054	759	88.9	3.4	275	260	310	266	25.3	22.3
Subject 4	1313	2089	12.3	3.9	274	333	206	297	25.7	30.9
Subject 5	1836	1444	10.5	3.6	336	300	375	385	28.1	22.9
Subject 6	2509	1675	41.6	11.1	274	362	373	375	32.7	34.5
Subject 7	2741	2443	10.8	3.7	369	255	244	277	30.4	37.3
Subject 8	2450	1550	10.7	5.9	286	335	495	250	37.8	38.3
Subject 9	2109	1463	32.9	30.8	169	253	311	265	26.5	26.1
Subject 10	3631	2741	29.1	10.2	374	405	295	181	39.1	38.7
Subject 11	2993	3210	7.8	2.8	187	156	246	237	34.9	36.6
Subject 12	2654	1167	12.0	4.0	270	269	250	423	34.1	33.5
Subject 13	1148	873	9.7	3.2	387	447	223	207	44.0	45.8
Intensity										
Subject 14	1614	1742	0.4	10.5	538	388	257	214	30.9	30.8
Subject 15	395	309	7.0	2.4	356	293	663	467	30.0	27.9
Subject 16	811	1262	2.5	1.8	329	274	209	221	32.2	24.4
Subject 17	174	66	1.5	3.9	521	394	451	418	30.4	24.2
Subject 18	1590	1239	2.4	11.7	331	276	360	364	50.8	55.9
Subject 19	836	582	7.1	3.6	570	565	368	365	30.8	26.3
Subject 20	275	545	11.1	9.2	275	236	281	200	27.8	33.1
Subject 21	714	1303	3.4	7.2	419	476	462	299	26.7	30.7
Subject 22	521	327	4.2	1.7	364	359	309	188	29.6	19.7
Subject 23	1372	1322	4.2	1.1	259	212	230	268	44.8	57.2
Subject 24	1317	1503	3.3	1.2	677	627	221	229	89.0	90.1
Subject 25	663	1249	1.5	5.3	558	506	180	273	25.4	26.9
Subject 26	1857	1602	2.2	1.4	211	199	327	255	24.5	19.9

*IGF-1 = insulin-like growth factor 1; Wk 1 = week 1; Wk 8 = week 8.

transferred to a personal computer and analyzed by the same investigator using Image J (version 1.45s; National Institutes of Health, Bethesda, MD, USA). The averaged values from both images within a specific region were used for statistical analysis. Using these procedures, measures of reliability had been determined for assessing the RF (MT: $ICC_{3,K} = 0.93$, $SEM_{3,K} = 0.17$, MD = 0.45 cm; CSA: $ICC_{3,K} = 0.88$, $SEM_{3,K} = 1.78$, MD = 4.60 cm²) and VL (MT: $ICC_{3,K} = 0.88$, $SEM_{3,K} = 0.16$, MD = 0.42 cm; CSA: $ICC_{3,K} = 0.99$, $SEM_{3,K} = 1.11$, MD = 3.05 cm²) musculature on ten active, resistance-trained men (25.3 ± 2.0 year; 90.8 ± 6.8 kg; 180.3 ± 7.1 cm). Individual measures (MT and CSA) of the RF and VL muscles are presented in Table 1.

Blood Sampling and Hormonal Analyses

During the resistance training period, blood samples were collected on the first day of week 1 (week 1) and week 8 (week 8), as previously described (21). Briefly, during each blood collection trial, participants reported to the Human

Performance Laboratory (HPL) 3 hours postprandial, at a time of day consistent with their normal training schedule. After a 15-minute equilibration period, baseline (BL) samples were collected and participants were then provided ~235 ml of chocolate milk or Lactaid (Lactaid[®] Chocolate Lowfat Milk; McNeil Nutritionals LLC, Ft. Washington, PA). Subsequently, participants completed their respective resistance exercise protocol. On completion of the resistance exercise protocol, an immediately postexercise (IP) blood sample was collected and then participants were provided their normal ~235 ml of chocolate milk or Lactaid post-exercise. Participants then remained in the HPL, lying in the supine position for the remaining blood sample collection time points: 30 minutes postexercise (30P) and 60 minutes postexercise (60P). All blood samples were analyzed for circulating concentrations of testosterone (T), cortisol (CORT), insulin-like growth factor (IGF-1), 22-kD growth hormone (GH), and insulin (INSL). To eliminate inter-assay variance, all samples for

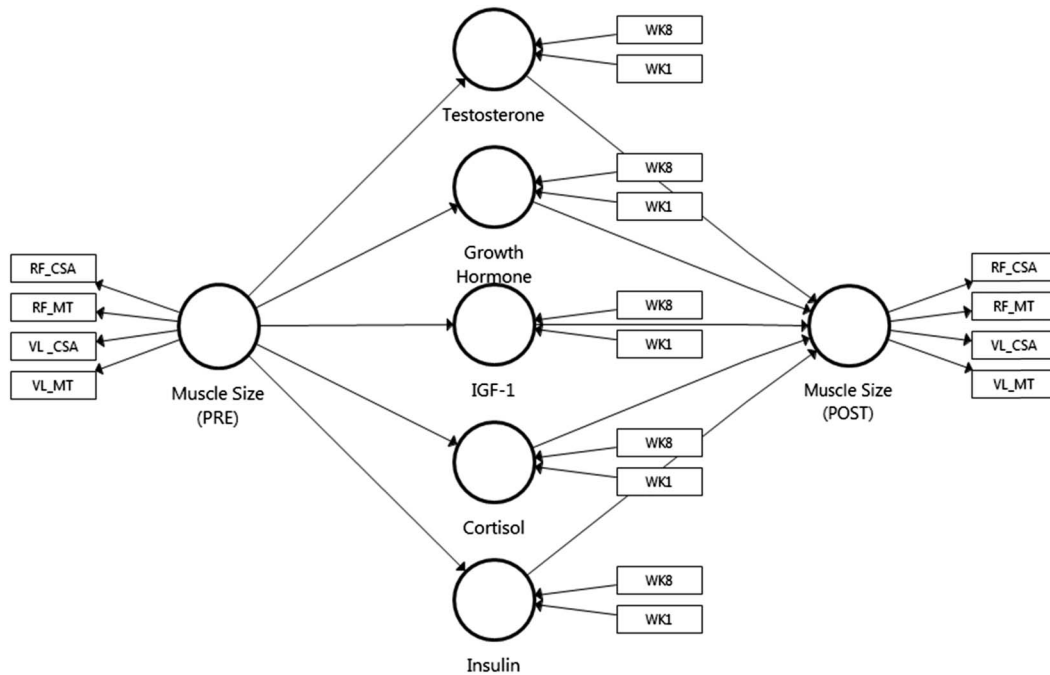


Figure 1. Model for the relationship between changes in muscle size and the endocrine response to resistance exercise. IGF-1 = insulin-like growth factor 1; RF_CSA = rectus femoris cross-sectional area; RF_MT = rectus femoris muscle thickness; VL_CSA = vastus lateralis cross-sectional area; VL_MT = vastus lateralis muscle thickness; WK 1 = week 1; WK 8 = week 8.

each assay were analyzed in duplicate in the same assay run by a single technician resulting in an average coefficient of variation of 3.74% for T, 4.03% for CORT, 6.77% IGF-1, 3.50% for GH, and 6.54% for INSL. The area under the curve (AUC), expressed in arbitrary units (au) through the trapezoidal method was calculated and used for statistical analysis. The individual endocrine responses to resistance exercise during week 1 and week 8 are presented in Table 2.

Statistical Analyses

Partial least squares structural equation modeling (PLS-SEM) was used to assess the relationships between muscle thickness and CSA and the endocrine response to resistance exercise. Figure 1 illustrates the inner and outer relationship models under investigation. Initially, the outer measurement model, which described the relationships between the collected indicator variables (i.e., endocrine response at week 1

and week 8, muscle thickness/CSA measures at PRE and POST) and their associated latent constructs was assessed using factor analysis or multiple linear regression for all reflective (i.e., collected measures of muscle size) and formative (i.e., collected endocrine response measures) constructs, respectively. Subsequently, the inner structural model (i.e., relationships between latent constructs) was evaluated using a consistent PLS-SEM algorithm (8). The quality of the model was assessed by its ability to explain variance (R^2 ; r-squared) and the statistical significance of the path coefficients (15). Interpretations of R^2 values were evaluated at the following levels: weak (0.190), moderate (0.333), and substantial (0.670). Statistical significance for each path coefficient was determined through bootstrapping using 1,000 iterations (9,31). Group differences in the model's quality were examined by an independent t -test using the means and standard error for R^2 from bootstrap analysis from each group and Equation 1 (22):

$$t = \frac{\text{Mean of } R^2(\text{Group 1}) - \text{Mean of } R^2(\text{Group 2})}{\sqrt{\text{Standard Error of } R^2(\text{Group 1})^2 + \text{Standard Error of } R^2(\text{Group 2})^2}} \quad (1)$$

TABLE 3. Significant pathways between muscle size and the endocrine response to resistance exercise.*

	Original sample	Bootstrap sample	Standard error	t	p
Muscle size (PRE) → Endocrine response					
Cortisol	0.449	0.428	0.296	1.519	0.129
Growth hormone	0.426	0.077	0.490	0.869	0.385
IGF-1	-0.030	-0.071	0.341	0.087	0.930
Insulin	-0.476	-0.251	0.450	1.058	0.290
Testosterone	0.467	0.428	0.231	2.022	0.043
Endocrine response → Muscle size (POST)					
Cortisol	0.083	0.105	0.193	0.429	0.668
Growth hormone	0.437	0.099	0.429	1.019	0.308
IGF-1	-0.184	-0.161	0.214	0.862	0.389
Insulin	-0.372	-0.157	0.347	1.074	0.283
Testosterone	0.617	0.491	0.287	2.146	0.032

*IGF-1 = insulin-like growth factor 1.

A criterion alpha level of $p \leq 0.05$ was used to determine statistical significance. Statistical Software (SmartPLS version 3.2.1; SmartPLS GmbH, Bönningstedt, Germany) was used for analyses of the statistical models. Post hoc power analyses of each significant model were performed using a publicly available calculator (32).

RESULTS

Resistance Training Program Comparisons

Programming characteristics, estimated dietary intakes, all training program outcomes and comparisons, as well as the endocrine response to resistance exercise at week 1 and

week 8 have been previously reported (21). Briefly, the average training volume load was significantly greater (28.4%) for VOL over INT, but no group differences were observed in relative caloric intake, relative protein intake, or changes in lower-body muscle size over the course of 8 weeks of resistance training. Significant group differences were observed in the endocrine response to training. At the onset of training (week 1), significantly greater GH (42.4%) and CORT (29.2%) responses to exercise were observed for VOL, whereas no group differences were observed for T, IGF-1, or INSL. At week 8, only CORT remained significantly greater (21.6%) for VOL.

TABLE 4. Group differences in pathway coefficients for the relationships between the endocrine response to resistance exercise and muscle size at POST.*

Endocrine response	Bootstrap sample	Standard error	t	p
Cortisol				
Volume	0.171	0.516	0.335	0.741
Intensity	−0.237	1.100		
Growth hormone				
Volume	−0.080	0.584	0.004	0.997
Intensity	−0.089	2.021		
IGF-1				
Volume	−0.426	0.432	0.086	0.932
Intensity	−0.167	2.986		
Insulin				
Volume	0.359	0.401	0.302	0.764
Intensity	−0.202	1.812		
Testosterone				
Volume	0.033	0.534	0.363	0.720
Intensity	0.881	2.275		

*IGF-1 = insulin-like growth factor 1.

Assessment of Model Quality

The consistent PLS-SEM algorithm revealed a substantial ability ($R^2 = 0.734$, $p < 0.001$) for muscle thickness/CSA (PRE) and the entire endocrine response in explaining variance in muscle thickness/CSA (POST). The power to observe this was 0.783 and variance inflation factors were all below 10, indicating no issues relating to multicollinearity. Bootstrap analysis indicated that significant ($p \leq 0.05$) pathways existed from muscle size at PRE to the T response and from the T response to muscle size at POST. No other pathways were observed to be significant. When the model was reanalyzed without T, the ability of the remaining model to explain variance in muscle size (POST) was reduced ($R^2 = 0.426$, $p = 0.014$). Further, no significant individual pathways were observed. Conversely, separate analyses of the model with GH ($R^2 = 0.75$, $p < 0.001$), CORT ($R^2 = 0.73$, $p < 0.001$), IGF-1 ($R^2 = 0.73$, $p < 0.001$), or INSL ($R^2 = 0.64$, $p < 0.001$) removed did not affect the model's ability to explain variance in muscle size (POST). All pathway coefficients, their standard error, and significance of the original model are presented in Table 3.

When the quality of the model was assessed in each group independently, improvements ($p < 0.001$) were observed for both VOL ($R^2 = 0.987$) and INT ($R^2 = 0.882$). However, no group differences in model quality were observed ($p = 0.496$). Group-wise comparisons of pathway coefficients and their standard error are presented in Table 4.

DISCUSSION

This study demonstrates the use of PLS-SEM to identify the relationships between several measures collected across multiple time points. Our major finding indicated that the endocrine response to resistance exercise, specifically testosterone, is related to muscle hypertrophy across 8 weeks of training. Previously, a strong correlation ($r = 0.76$) between the testosterone response to resistance exercise and muscle hypertrophy had been reported in one study (1), but not in others ($r = 0.06$ – 0.14 ; $p > 0.05$) (23,40). The lack of consistency between studies might be explained, in part, by differences in how the relationships were assessed. Ahtiainen et al. (1) related change scores (muscle size and testosterone response), whereas the other 2 studies related the change in muscle size to an averaged testosterone response (23) or the response from a single time point (23,40). The important distinction is that relating 2 sets of change scores assumes that initial scores lack importance, whereas the later studies ignore potentially important variations in the endocrine response across the training period. In contrast, PLS-SEM does not alter the data when assessing the relationships between indicator variables and their latent concept or between latent concepts (6,14). Consequently, PLS-SEM provides a more accurate assessment of the relationships in question. To date, this is the first study to examine the relationships between the endocrine response to resistance exercise and muscle hypertrophy in this manner.

Our results indicated that 73.4% of the variance in muscle size after 8 weeks of resistance training could be explained by baseline muscle size and the endocrine response (i.e., CORT, GH, IGF-1, INSL, and T) across training. However, T was the only significant pathway. During rest, exogenously elevated concentrations in circulating testosterone have been demonstrated to enhance protein synthesis and inhibit protein breakdown within skeletal muscle (7), and to suppress the catabolic effects of elevated cortisol concentrations (42). In response to resistance exercise, the specific role of transitory elevations in testosterone for promoting muscle growth remains unclear. Previously, West and colleagues (39) reported no enhancement on anabolic signaling or acute postexercise muscle protein synthesis from exercise-induced elevations in testosterone. Although this may be true, it does not eliminate the testosterone (or any hormone) response from being physiologically important for muscle hypertrophy. Our results provide evidence that the exact training stimulus may not change the relationship between the exercise-induced endocrine response, specifically testosterone, and muscle hypertrophy. Some investigators have suggested a nongenomic (i.e., independent of its receptor) role where testosterone stimulates transient increases in intracellular calcium (10), which may temporarily elevate maximal force production (16). In this capacity, exercise-induced elevations in testosterone might enable greater training intensity and volume load during resistance exercise, which seems to be more beneficial for stimulating muscle hypertrophy in a resistance-trained population (21). Regardless of the mechanism, our findings suggest that postexercise testosterone elevations do influence muscle hypertrophy.

The remaining model (without testosterone) was capable of explaining 42.6% of the variance in muscle thickness/CSA after 8 weeks of resistance training. However, there were no significant pathways observed amongst the remaining hormones (i.e., CORT, GH, IGF-1, or INSL), which may imply that a synergistic endocrine response is more influential of muscle hypertrophy than the individual responses from these specific hormones. Though evidence of interdependent relationships between hormones supports this notion, there is no evidence of muscle hypertrophy being affected. For instance, growth hormone concentrations may be partially responsible for IGF-1 release (13), but circulating IGF-1 concentrations have not been previously related to muscle hypertrophy (23,40). Rather, its anabolic effect may be dependent on its uptake into skeletal muscle (25), which was not examined in this study. Circulating cortisol concentrations are also known to affect protein synthesis by competing with testosterone within the muscle cell (42). However, transient changes in cortisol concentrations have not been shown to affect protein synthesis (30). Finally, insulin is known to regulate the same protein synthesis pathways affected by T and IGF-1 (33), but its role immediately after exercise seems to be highly dependent on dietary intake surrounding the workout (17). Thus, it is possible that an

ideal exercise-induced hormonal milieu for muscle hypertrophy exists, but the present model was not capable of distinguishing it beyond the influence of T. This may have been the consequence of data collection times (i.e., blood samples were only collected during week 1 and week 8) affecting the sensitivity of the model to detect the influence of measures with limited contributions. Assessing the endocrine response on a greater number of occasions (>2) may afford a better opportunity for PLS-SEM to maximize the variance amongst these latent constructs (e.g., CORT, GH, IGF-1, and INSL) and thus determine their relationship to muscle hypertrophy (6,14).

PRACTICAL APPLICATIONS

Traditional statistical measures do not adequately assess the relationships between multiple variables that exist across time. This investigation demonstrates a unique method for analyzing these types of relationships without the need for transforming data. Our findings indicate that baseline muscle size and the hormonal response to resistance exercise are related to muscle hypertrophy after 8 weeks of training. In particular, exercise-induced testosterone concentrations seem to be more influential of hypertrophy in comparison to the cortisol, growth hormone, IGF-1, and insulin responses to resistance exercise. Further, the observed relationships seem to remain consistent regardless of whether resistance training emphasizes training volume or intensity.

REFERENCES

- Ahtiainen, JP, Pakarinen, A, Alen, M, Kraemer, WJ, and Häkkinen, K. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. *Eur J Appl Physiol* 89: 555–563, 2003.
- Ahtiainen, JP, Pakarinen, A, Kraemer, WJ, and Häkkinen, K. Acute hormonal and neuromuscular responses and recovery to forced vs maximum repetitions multiple resistance exercises. *Int J Sports Med* 24: 410–418, 2003.
- Baechle, T, Earle, R, and Wathen, M. Resistance training. In: *Essentials of Strength Training and Conditioning*. Champaign, IL: Human Kinetics, 2008. pp. 381–410.
- Brandenburg, JE and Docherty, D. The effects of accentuated eccentric loading on strength, muscle hypertrophy, and neural adaptations in trained individuals. *J Strength Cond Res* 16: 25–32, 2002.
- Cănuță, M, Crișan, LG, Vulturar, R, Opre, A, and Miu, AC. Emotional non-acceptance links early life stress and blunted cortisol reactivity to social threat. *Psychoneuroendocrinology* 51: 176–187, 2015.
- Cassel, C, Hackl, P, and Westlund, AH. Robustness of partial least-squares method for estimating latent variable quality structures. *J Appl Stat* 26: 435–446, 1999.
- Crowley, MA and Matt, KS. Hormonal regulation of skeletal muscle hypertrophy in rats: The testosterone to cortisol ratio. *Eur J Appl Physiol Occup Physiol* 73: 66–72, 1996.
- Dijkstra, TK and Schermelleh-Engel, K. Consistent partial least squares for nonlinear structural equation models. *Psychometrika* 79: 585–604, 2014.
- Efron, B and Tibshirani, RJ. Random samples and probabilities. In: *An Introduction to the Bootstrap*. Boca Raton, FL: Chapman & Hall/CRC Press, 1993. pp. 17–28.
- Estrada, M, Espinosa, A, Müller, M, and Jaimovich, E. Testosterone stimulates intracellular calcium release and mitogen-activated protein kinases via a G protein-coupled receptor in skeletal muscle cells. *Endocrinology* 144: 3586–3597, 2003.
- Gefen, D, Straub, D, and Boudreau, M-C. Structural equation modeling and regression: Guidelines for research practice. *Commun Assoc Inf Syst* 4: 7, 2000.
- Gonzalez, AM, Hoffman, JR, Townsend, JR, Jajtner, AR, Boone, CH, Beyer, KS, Baker, KM, Wells, AJ, Mangine, GT, and Robinson, EH. Intramuscular anabolic signaling and endocrine response following high volume and high intensity resistance exercise protocols in trained men. *Physiol Rep* 3: e12466, 2015.
- Gregory, SM, Spiering, BA, Alemany, JA, Tuckow, AP, Rarick, KR, Staab, JS, Hatfield, DL, Kraemer, WJ, Maresch, CM, and Nindl, BC. Exercise-induced insulin-like growth factor I system concentrations after training in women. *Med Sci Sports Exerc* 45: 420–428, 2013.
- Haenlein, M and Kaplan, AM. A beginner's guide to partial least squares analysis. *Understanding Stat* 3: 283–297, 2004.
- Hair, JF, Black, WC, Babin, BJ, Anderson, RE, and Tatham, RL. Multiple regression analysis. In: *Multivariate Data Analysis*. Upper Saddle River, NJ: Prentice Hall, 2006. pp. 206.
- Hamdi, M and Mutungi, G. Dihydrotestosterone activates the MAPK pathway and modulates maximum isometric force through the EGF receptor in isolated intact mouse skeletal muscle fibres. *J Physiology* 588: 511–525, 2010.
- Hulmi, JJ, Volek, JS, Selänne, H, and Mero, AA. Protein ingestion prior to strength exercise affects blood hormones and metabolism. *Med Sci Sports Exerc* 37: 1990–1997, 2005.
- Kraemer, WJ, Marchitelli, L, Gordon, SE, Harman, E, Dziados, JE, Mello, R, Frykman, P, McCurry, D, and Fleck, SJ. Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol* 69: 1442–1450, 1990.
- Kraemer, WJ and Ratamess, NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med* 35: 339–361, 2005.
- Kuceyeski, A, Kamel, H, Navi, BB, Raj, A, and Iadecola, C. Predicting future brain tissue loss from white matter connectivity disruption in ischemic stroke. *Stroke* 45: 717–722, 2014.
- Mangine, GT, Hoffman, JR, Gonzalez, AM, Townsend, JR, Wells, AJ, Jajtner, AR, Beyer, KS, Boone, CH, Miramonti, AA, and Wang, R. The effect of training volume and intensity on improvements in muscular strength and size in resistance-trained men. *Physiol Rep* 3: e12472, 2015.
- Maruyama, GM. Variations on the basic latent variable structural equation model. In: *Basics of Structural Equation Modeling*. Thousand Oaks, CA: Sage Publications, 1997. pp. 259.
- McCall, GE, Byrnes, WC, Fleck, SJ, Dickinson, A, and Kraemer, WJ. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. *Can J Appl Physiol* 24: 96–107, 1999.
- Mitchell, CJ, Churchward-Venne, TA, Bellamy, L, Parise, G, Baker, SK, and Phillips, SM. Muscular and systemic correlates of resistance training-induced muscle hypertrophy. *PLoS One* 8: e78636, 2013.
- Ochi, E, Ishii, N, and Nakazato, K. Time course change of IGF1/Akt/mTOR/p70s6k pathway activation in rat gastrocnemius muscle during repeated bouts of eccentric exercise. *J Sports Sci Med* 9: 170, 2010.
- Ratamess, NA, Alvar, BA, Evetoch, TK, Housh, TJ, Kibler, WB, Kraemer, WJ, and Triplett, NT. American college of sports medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 41: 687, 2009.
- Ratamess, NA, Kraemer, WJ, Volek, JS, Maresch, CM, Vanheest, JL, Sharman, MJ, Rubin, MR, French, DN, Vescovi, JD, and Silvestre, R. Androgen receptor content following heavy resistance exercise in men. *J Steroid Biochem Mol Biol* 93: 35–42, 2005.

28. Schoenfeld, BJ, Ratamess, NA, Peterson, MD, Contreras, B, Sonmez, G, and Alvar, BA. Effects of different volume-equated resistance training loading strategies on muscular adaptations in well-trained men. *J Strength Cond Res* 28: 2909–2918, 2014.
29. Schwab, R, Johnson, GO, Housh, TJ, Kinder, JE, and Weir, J. Acute effects of different intensities of weight lifting on serum testosterone. *Med Sci Sports Exerc* 25: 1381–1385, 1993.
30. Short, KR, Bigelow, ML, and Nair, KS. Short-term prednisone use antagonizes insulin's anabolic effect on muscle protein and glucose metabolism in young healthy people. *Am J Physiology Endocrinol Metab* 297: E1260–E1268, 2009.
31. Shrout, PE and Bolger, N. Mediation in experimental and nonexperimental studies: New procedures and recommendations. *Psychol Methods* 7: 422, 2002.
32. Soper, DS. *Post-hoc Statistical Power Calculator for Multiple Regression [Software]*. Available at: <http://www.danielsoper.com/statcalc>. Accessed April 14, 2016.
33. Tixier, V, Bataillé, L, Etard, C, Jagla, T, Weger, M, DaPonte, JP, Strähle, U, Dickmeis, T, and Jagla, K. Glycolysis supports embryonic muscle growth by promoting myoblast fusion. *Proc Natl Acad Sci U S A* 110: 18982–18987, 2013.
34. Vincent, W and Weir, J. Correlation and bivariate regression. In: *Statistics in Kinesiology*. Champaign, IL: Human Kinetics, 2012, pp. 114.
35. Walker, S, Santolamazza, F, Kraemer, W, and Häkkinen, K. Effects of prolonged hypertrophic resistance training on acute endocrine responses in young and older men. *J Aging Phys Act* 23: 230–236, 2014.
36. Weir, JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* 19: 231–240, 2005.
37. West, DW, Burd, NA, Staples, AW, and Phillips, SM. Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process. *Int J Biochem Cell Biol* 42: 1371–1375, 2010.
38. West, DW, Burd, NA, Tang, JE, Moore, DR, Staples, AW, Holwerda, AM, Baker, SK, and Phillips, SM. Elevations in ostensibly anabolic hormones with resistance exercise enhance neither training-induced muscle hypertrophy nor strength of the elbow flexors. *J Appl Physiol* (1985) 108: 60–67, 2010.
39. West, DW, Kujbida, GW, Moore, DR, Atherton, P, Burd, NA, Padzik, JP, De Lisio, M, Tang, JE, Parise, G, and Rennie, MJ. Resistance exercise-induced increases in putative anabolic hormones do not enhance muscle protein synthesis or intracellular signalling in young men. *J Physiol* 587: 5239–5247, 2009.
40. West, DW and Phillips, SM. Associations of exercise-induced hormone profiles and gains in strength and hypertrophy in a large cohort after weight training. *Eur J Appl Physiol* 112: 2693–2702, 2012.
41. Yang, CH, Lin, YD, Wu, SJ, Chuang, LY, and Chang, HW. High order gene-gene interactions in eight single nucleotide polymorphisms of renin-angiotensin system genes for Hypertension Association Study. *Biomed Res Int* vol. 2015: 11 pages, 2015. doi: 10.1155/2015/454091.
42. Zhao, W, Pan, J, Zhao, Z, Wu, Y, Bauman, WA, and Cardozo, CP. Testosterone protects against dexamethasone-induced muscle atrophy, protein degradation and MAFbx upregulation. *J Steroid Biochem Mol Biol* 110: 125–129, 2008.