

Elderly Patients and High Force Resistance Exercise—A Descriptive Report: Can an Anabolic, Muscle Growth Response Occur Without Muscle Damage or Inflammation?

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ABSTRACT

Background and Purpose: Elderly individuals participate in resistance exercise to induce an anabolic response and grow muscle to help overcome functional deficits. It is thought that a muscle damage and inflammatory response to resistance exercise is a necessary prerequisite for an anabolic and muscle growth response. **Methods:** This is a descriptive study of 11 elderly individuals in rehabilitation who underwent a 2-3x/week high force resistance exercise that used eccentric contractions. Serum measures of muscle damage, inflammation, and an anabolic response are reported along with changes in muscle mass as measured with dual energy X-ray absorptiometry. **Results:** Negative work increased >3-fold during the 11 weeks of resistance exercise. There were no significant changes in the damage measure of serum creatine kinase (pretraining: 18.5 ± 1.2 Sigma units/ml; post-training: 19.2 ± 1.1 Sigma units/ml). Pro-inflammatory tumor necrosis factor- α values remained within normal range (<4.0 pg/ml) throughout the 11 weeks of training. A nonsignificant trend for an anabolic increase (65%) in insulin like growth factor-1 was noted along with a significant increase (6%) in thigh muscle mass. **Conclusions:** Neither damage, nor inflammation appear to be prerequisites for inducing anabolic and muscle growth responses in elderly individuals undergoing a high force resistance exercise with eccentric contractions.

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INTRODUCTION

Resistance strength training can increase muscle size in older individuals¹⁻⁸, although the muscle hypertrophy response is both inconsistent^{3,4,7} and often blunted in magnitude^{7,9} relative to that reported in younger individuals. Customary thinking is that muscle damage and the inflammatory response that follows are coupled to, and perhaps serve as necessary precursors for, an anabolic response and muscle hypertrophy.¹⁰⁻¹⁴ With that, much work has been done to identify the 'best' exercise regimen to optimize muscle force production and the resultant hypertrophy and improved mobility in elderly individuals. Because exercises that induce eccentric contractions can produce significantly higher forces than combined eccentric and concentric exercises, it may be the ideal stimulus to induce hypertrophy.¹⁵⁻¹⁹ While high eccentric forces produce a maximum stimulus for muscle hypertrophy, as well as muscle damage,²⁰⁻²⁵ these forces may be the stimulus needed to promote regenerative satellite cell and proinflammatory activity which includes a chemotactic attraction of myogenic stem cells essential for muscle growth.²⁶

The anabolic mediator insulin-like growth factor-1 (IGF-1) is a key regulator of muscle hypertrophy and muscle function.^{27,28} IGF-1 is produced in response to growth hormone release from the pituitary gland.^{29,30} After binding to its receptor, growth hormone induces the local production of IGF-1 by autocrine and paracrine mechanisms.

For aging adults, both the regenerative muscle damage/inflammation and anabolic IGF-1 responses following resistance exercise are thought to be suppressed, inhibiting the muscle hypertrophy response and further reinforcing the apparent linkage between damage and hypertrophy. Consistent with the 'damage preceding hypertrophy' hypothesis, eccentric contractions typically produce the most muscle damage.³¹ While eccentric contractions can cause substantial muscle damage, there is no evidence that they necessarily have to cause damage. That is, when progressively exposed to a ramped protocol of eccentric contractions and increasing levels of negative work, muscles of young individuals respond by increasing in size and strength without any demonstrable injury or impairment to the muscle.^{17,32} It is unclear, however, if aging adults, many of whom

can ill-afford further muscle impairment or systemic inflammation, respond in a similar fashion.

In this short report we describe whether a resistance exercise program can lead to an anabolic, muscle growth, response without inducing a proinflammatory or muscle damage response. The resistance exercise regimen exposed older individuals in rehabilitation to high force eccentric muscle contractions via a progressively increased force production protocol.

METHODS

Participants

Eleven high fall risk older adult subjects (mean age=78 years, range=70-89 years, 5 male, 6 female) enrolled in a phase II-IV cardiopulmonary rehabilitation program consented to participate according to IRB regulations. All individuals were characterized as being at a high fall risk as determined by a timed up and go result >14 seconds.³³ Multiple comorbidities, and their commensurate medical treatments, characterize the participant group (Table 1).

High Force Resistance Exercise with Eccentric Contractions

This heterogeneous sample population experienced high force eccentric contractions using a motorized lower extremity ergometer that provided real time feedback as to the

work (quantified as negative work) performed. The eccentric ergometer and ramped protocol have been described previously.^{17,18} The resistance exercise program consisted of lower extremity eccentric exercise 2-3x per week for 11 weeks (Figure 1). During the initial progressive increase in force production, the target perceived exertion increased gradually during weeks 1 through 5 from “very very light” to “somewhat hard” where it was maintained during weeks 6 through 11. The eccentric muscle activity, and the resultant negative work performed, was a function of the perceived exertion of training and the duration of training (3-20 minutes), thereby inducing increases in training work-loads (Table 2). For the final 6 weeks, while the perceived exertion remained constant, the work loads on the eccentric ergometer increased ~3 fold; the total force production measured as negative work increased from an group average of 70.3 (± 12.4 SE) Kjoules to 232.4 (± 27.2) Kjoules over the final 6 weeks.

Blood Measures of Muscle Damage, Inflammation, and IGF-1

Muscle damage and inflammation were assessed as described previously.³⁴⁻³⁶ Plasma creatine kinase (CK) was measured using a CK kit (Sigma 520C) with a microplate reader. All blood samples were analyzed in duplicate. Quality control for the CK measures was assured by assessing the linearity of

Table 1. Experimental participant cohort. This heterogeneous group of elderly individuals is representative of patients seen in rehabilitation for exercise.

Subject	Age	Gender	Cardiovascular diagnoses and Co-morbidities	Exercise Risk *
1	77	male	coronary artery bypass graft x1; hypertension	Low
2	78	male	angioplasty and stent x 2	Medium
3	84	male	valve insufficiency and replacement; prostate cancer	High
4	71	male	myocardial infarction x2; coronary artery bypass graft x1; peripheral vascular disease; aortic aneurysm repair; rheumatoid arthritis; prostate cancer	Medium
5	70	male	coronary artery bypass graft x4; prostate cancer; type II diabetes mellitus	Medium
6	79	female	valve replacement x2; Hip open reduction internal fixation	Low
7	74	female	hypertension; chronic heart failure	Low
8	89	female	valve replacement x2; chronic heart failure	Medium
9	80	female	valve insufficiency; chronic heart failure	Low
10	84	female	myocardial infarction; hypertension	Low
11	71	female	hypertension; chronic heart failure	Low

***Low** = no LV dysfunction (LVEF>50%), no resting or stress-induced dysrhythmias, uncomplicated MI, CABG, PTCA/stent, Normal hemodynamic response to moderate exercise, asymptomatic, Functional capacity of 7 METS 3 weeks post event ETT.

***Medium** = moderately impaired left ventricular function (LVEF 40-49%), symptoms (e.g., angina) with moderate exercise, failure to comply with previous exercise prescription, inability to monitor self, functional capacity of 5-6.9 METS 3 weeks post event ETT.

***High** = decreased left ventricular function (LVEF<40%), survivor of cardiac arrest, complex ventricular dysrhythmias at rest or with exercise, complicated MI, CABG, cardiogenic shock, abnormal hemodynamics with exercise, angina with low level activity, functional capacity < 5 METS on 3 weeks post event ETT

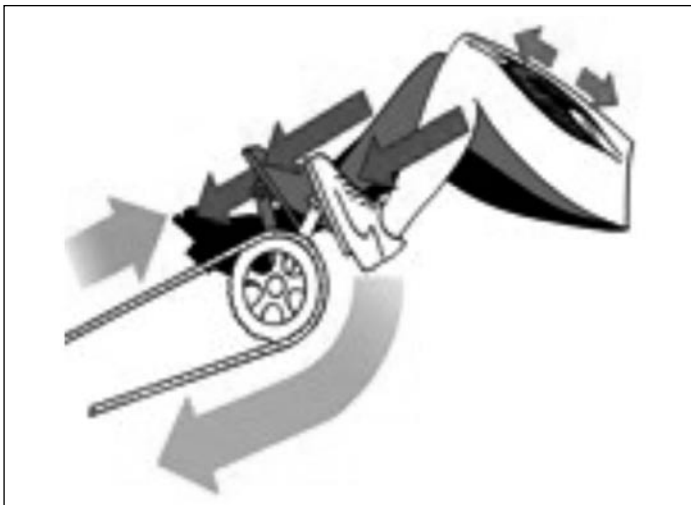


Figure 1. The eccentric ergometer used for high muscle force resistance exercise. As the motor rotates the pedals at a set speed in a reverse direction (large arrows) the participant attempts to slow down the reverse moving pedals by applying force to the pedals (medium arrows). Because the magnitude of force produced by the motor exceeds that produced by the participant, the pedals continue backward, resulting in eccentric lengthening of the eg, quadriceps muscles (small arrows).

***Negative work is the product of a muscle’s force production and change (Δ) in length. When an external force exceeds the muscle’s force production, the muscle lengthens away from center (ie, eccentric Δ length). This Δ length has a negative sign, hence work is negative.**

the standard curves ($r > 0.98$) and running positive control standards supplied by the manufacturer. Tumor necrosis factor (TNF) $-\alpha$ was measured by enzyme linked immunosorbent assay (ELISA) (Ultra-sensitive kits, Biosource Inc., Camarillo, Calif) as a measure of the proinflammatory cytokine. Total IGF-1 was also measured by ELISA to assess the anabolic response. Inter- and intra-assay coefficients of variation are less than 9% and 5%, respectively.

The blood measures were made at 3 time points (Initial=1st week before training was initiated; Mid=5th week of training; Final=11th week of training) from 10 ml venous blood samples. The mid-5th week and final-11th week measures of TNF- α occurred immediately before and 3 hours after a training ses-

sion; and the CK measures occurred immediately before and 48 hours after a training session. These postexercise session blood sample measures were meant to coincide with respective peak inflammatory and damage responses, if any.

Muscle Size Measurement

Whole muscle mass (g/cm^2) of the muscle tissue region of interest approximated by the knee extensor, knee flexor, leg adductor, and leg abductor muscle groups, was measured via dual energy X-ray absorptiometry (DXA) using the densitometer (DPX-IQ, GE-Lunar, Madison, Wisc) before and after 11 weeks of training. Participants were positioned according to the manufacturer’s standardized recommendations and scanned twice at each time period (pre- and posttraining). The mean of the two measurements was used in all statistical analyses. Scan analysis was done by one certified technician. The calibration of the densitometer was checked daily against a standard calibration block supplied by the manufacturer. The coefficient of variation was 0.6%. Lean soft tissue mass around the femur region of interest was measured minus the fat and bone masses and reported as a relative change in muscle mass from pre- to posttesting.

Statistical Analysis

Data were analyzed with SPSS Version 13.0 (SPSS Inc, Chicago, Ill). In all cases, the assumptions of normality and homogeneity of variance were met and parametric tests were performed. Each dependent variable was analyzed using separate one-way repeated measures analyses of variance (with one within subject factor [time]). The level of significance was set at $p < 0.05$ to test if muscle damage and inflammatory responses, if any, were consistent with that reported in the literature for both TNF- α and CK. Our expectation, however, was that a progressively increased, ramped, exercise protocol would not induce these responses. With that, we expected to be underpowered for the damage and proinflammatory variables, ie, it would have required >450 subjects at a power level of 0.80 to see statistically significant changes.

RESULTS

Muscle Damage (CK), Inflammation (TNF- α) and Anabolic Response (IGF-1)

There were no significant changes in either CK or the pro-inflammatory cytokine TNF- α when serum was examined over

Table 2. Perceived Exertion and Eccentric Resistance Exercise Progression (frequency and duration) Over the 11 Week Training Period

Week	Times/Week	Training Duration	Rating of Perceived Exertion
1	2	3-5 minutes	7 (very, very light)
2-4	3	5-15 minutes	9 (very light) to 11 (fairly light)
5	3	10-15 minutes	11-13 (fairly light to somewhat hard)
6-10	3	12-20 minutes	11-13 (fairly light to somewhat hard)
11	3	12-20 minutes	11-13 (fairly light to somewhat hard)

the 11 week training period. The week 1, initial mean CK values, 18.5 ± 1.2 Sigma units/ml, mid-training values, 18.7 ± 1.4 Sigma units/ml at week 5, and the 11 week posttraining values 19.2 ± 1.1 Sigma units/ml were not statistically different ($p > 0.05$). At all time points examined, no increase in CK was observed as the CK values remained within the normal range, ie, well below (approximately an order of magnitude) the concentration reported in other studies following an acute, high eccentric muscle force exercise bout. A 10 to 50 fold increase in CK is commonly observed in younger populations 2 days after an acute episode of high muscle force eccentric exercise.^{34,37}

Figure 2 outlines the results of the proinflammatory measurement. The TNF- α value of approximately 2 pg/ml was also well within the range of normal values, as specified by the manufacturer (Biosource), and similar to the pre-exercise value reported by Toft et al³⁸ in a group of elderly individuals of similar age to those in our study. Thus, the high eccentric muscle force exercise in our study did not cause a significant increase in proinflammatory cytokine activity. The TNF- α values remained within the normal non-inflammatory range reported by Biosource throughout the 11 week exercise training period.^{39,40} Two of the 11 subjects had elevated values of TNF- α (ie, > 3.8 pg/ml) at the beginning of the study. Interestingly, their values decreased by the midpoint of the study and were well within normal at the 11th week. The increase in TNF- α after exercise at week 11 was not statistically significant.

Since an anabolic upregulated IGF-1 response has been implicated in muscle mass augmentation, we investigated the effect of chronic high eccentric muscle force exercise on total serum IGF-1 (Figure 3). Initial IGF-1 levels in the older individuals were lower than normal young volunteers (< 40 ng/ml), and this is consistent with other observations that IGF-1 is generally

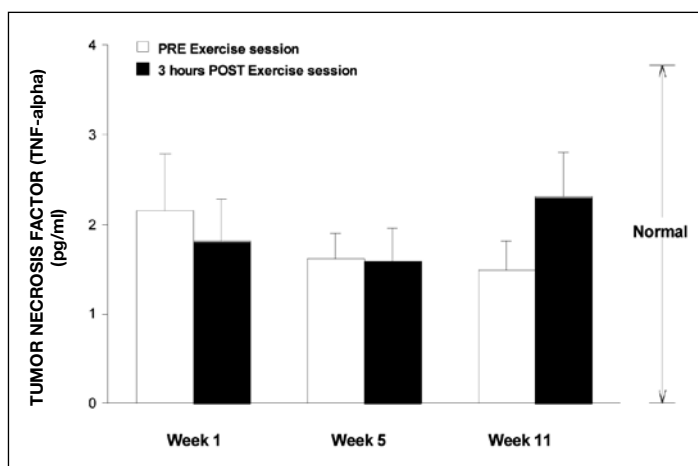


Figure 2. Tumor necrosis factor (TNF)- α (pg/ml) at the initial, pre-training time point (week 1), at the 5th week of training and the last week of training (week 11). The TNF- α levels stayed within normal limits throughout the course of the study, both prior to an eccentric exercise session (open bars) or three hours post exercise session (filled bars). The TNF- α levels are consistent to those reported in elderly subjects.^[38] Error bars = 1 SEM.

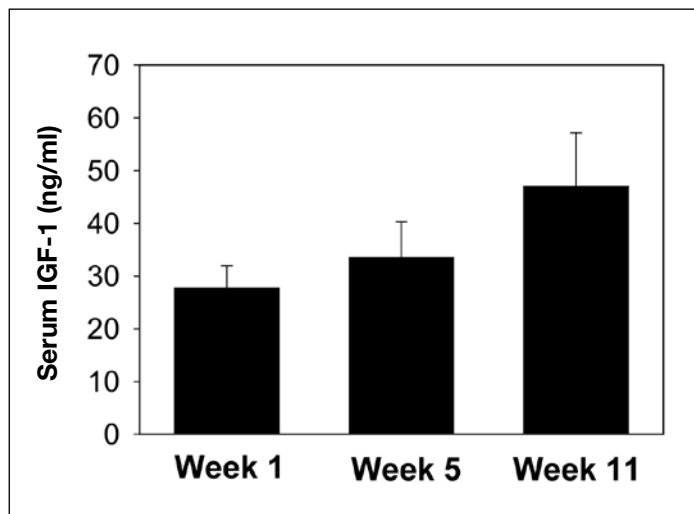


Figure 3. Total IGF-1 (ng/ml) from serum prior to (week 1) any eccentric resistance training, and at 5 and 11 weeks of high eccentric force negative work. High force eccentric training induced an apparent trend toward increasing (65%) total serum IGF-1 levels as measured in duplicates by enzyme linked immunosorbent assay (ELISA). Error bars = 1 SEM.

low for aging adults.⁴¹ However, upon completion of the training period there was a trend noted in serum IGF-1 levels with initial week 1 levels increasing 65% ($p > 0.05$) by the end of training, paralleling the progressive increase in negative work over the 11 weeks. We were underpowered (0.77) with this anabolic measure and predict that a sample of 12 to 15 individuals would have been required to achieve statistical significance at an alpha level of 0.05. Also, we could not detect sex differences with this very small sample size as the variance between subjects exceeds that which would be detectable between sexes.

Muscle Size Measurement

DXA evaluations following exercise training revealed a statistically significant ($P < 0.05$) 6% increase in the combined muscle mass of the knee flexors and extensors in this sample of frail aging adults.

DISCUSSION

A proinflammatory reaction to muscle damage is a normal physiologic response and a necessary part of the healing process. In the muscle literature, inflammation has been considered essential for inducing anabolic changes and for the regeneration and hypertrophy of muscle.⁴² It may be that a blunted suite of responses, ie, damage, inflammation, anabolic and muscle growth, are typical of older exercisers though this has yet to be unanimously corroborated.

High-force eccentric contractions, when performed by individuals who are naïve to the task, results in myofibrillar damage and inflammation, ie, promoting significant CK and TNF- α releases acutely.^{39,40} In this study with elderly individuals, however, the damage and pro-inflammatory cytokine markers never increased above the normal values over the course

of training despite the high eccentric forces and negative work loads generated during training. Rather, the progressive, gradually increasing exercise resulted in a trend toward increasing total IGF-1 in the serum and an increase in muscle mass. It is important to note that resistance exercises biased toward eccentric muscle contractions can induce high muscle forces while at low metabolic costs (see LaStayo⁴³ and Lindstedt⁴⁴ for reviews). In fact, the uncoupling of exertion and muscle force production is the key to any eccentric intervention designed to maximize muscle growth in older, frail individuals with comorbid conditions.^{18,45-48} Importantly during the eccentric training, energy was not 'expended,' but rather it was absorbed while force production in the muscle was undoubtedly high. It is important to emphasize that damage is the consequence of high force production by naïve muscle, yet hypertrophy is the consequence of repeated exposure to high force (ie, muscle overload). By gradually ramping up the negative workload, it is possible to completely uncouple the damage from the beneficial effects of high muscle force production.

It remains unclear, however, if the IGF-1 response in aging muscle experiencing an overload is blunted or non-existent as our results due to the small sample size. Others have documented increased serum IGF-1 anabolic responses in aging adults following 10 weeks⁴⁹ and 8 months⁵⁰ of resistance exercise, while other studies of 8 weeks to 6 months report no change in circulating IGF-1 in this age group.^{41,51-53} Repeated eccentric contractions, however, do induce an increase in IGF-1 in a younger population.⁵⁴ Systemic levels of IGF-1 in the serum can regulate an anabolic muscle hypertrophy response. The local production of IGF-1, and upregulation of specific muscle isoforms, however, are now generally associated with this hypertrophic response, but the increased serum level of IGF-1 is still considered an anabolic stimulus.^{27,55} Present literature suggests that liver production of IGF-1 is not increased with age,^{30,56,57} that liver IGF-1 is not an absolute necessity for muscle growth,⁵⁸ and that muscle-specific IGF-1 can be produced in response to eccentric contractions.⁵⁴ In addition, animal studies have indicated the loss of the pituitary gland and subsequent loss of GH release does not preclude muscle hypertrophy, suggesting that this process can occur independent of GH release.^{59,60} These reports, in combination with our data, suggest that the possible source of increased circulating IGF-1 in this aging adults might be from the muscle itself.

In support of our contention that an anabolic response occurred without an inflammatory or damage response, the increasing IGF-1 in the serum following a high force eccentric regimen was coupled with significant increases in leg muscle mass. This is an important clinical finding as aging individuals cannot afford a systematic inflammatory response nor any damage to muscle during rehabilitation, as their locomotor system is often already impaired and contributing to disability. When coupled with the previously reported 60% increase in both quadriceps muscle fiber cross sectional area and isometric strength in this same study population¹⁸ we suggest an anabolic muscle growth response occurred. The difference in DXA

muscle mass values and the muscle fiber cross sectional areas reported previously likely reflects the direct measurement of all muscles about the femur with DXA (including the adductors and hamstrings) in contrast to the small sample of the quadriceps (the muscle group directly loaded with the exercise mode) muscle fibers acquired with the biopsy.

Questioning the concept that muscle damage and pro-inflammatory activity are requisite responses to successful resistance exercise regimens is clinically important as the resistance exercise prescription for aging individuals is based on anticipated physiologic changes underlying muscle growth. While challenging traditional wisdom, our data does validate the need to more formally test whether an anabolic response of the muscle of aging individuals can occur without an inflammatory response resulting from damage. These data provide reasonable justification for larger, randomized and controlled studies which can test this hypothesis with more rigor.

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Conflicts of Interest Declaration:

The authors acknowledge they have no commercial interest conflicts associated with this manuscript.

REFERENCES

1. Fiatarone MA, Marcs EC, Ryan ND, et al. High-intensity strength training in nonagenarians. Effects on skeletal muscle. *JAMA*. 1990;263:3029-3034.
2. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of VO₂max in older men. *J Appl Physiol*. 1990;68:329-333.
3. Campbell WW, Crim MC, Young VR, et al. Effects of resistance training and dietary protein intake on protein metabolism in older adults. *Am J Physiol*. 1995;268:E1143-1153.
4. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330:1769-1775.
5. Hakkinen K, Alen M, Lakkinen M, et al. Neuromuscular adaptation during prolonged strength training, detraining and re-strength-training in middle-aged and elderly people. *Eur J Appl Physiol*. 2000;83:51-62.
6. Frontera WR, Meredith CN, O'Reilly KP, Knugttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol*. 1988;64:1038-1044.
7. Bamman MM, Ragan RC, Kim JS, et al. Myogenic protein expression before and after resistance loading in 26- and 64-yr-old men and women. *J Appl Physiol*. 2004;97:1329-1337.
8. Hunter GR, McCarthy JP, Bamman MM. Effects of resistance training on older adults. *Sports Med*. 2004;34:329-348.
9. Welle S, Totterman S, Thornton C. Effect of age on muscle

- hypertrophy induced by resistance training. *J Gerontol A Biol Sci Med Sci*.1996;51:M270-275.
10. Goldspink G. Gene expression in muscle in response to exercise. *J Muscle Res Cell Motil*, 2003;24:121-126.
 11. Evans WJ, Cannon JG. The metabolic effects of exercise-induced muscle damage. *Exerc Sport Sci Rev*. 1991;19:99-125.
 12. Folland JP, Irish CS, Roberts JC, et al. Fatigue is not a necessary stimulus for strength gains during resistance training. *Br J Sports Med*. 2002;36:370-373; discussion 374.
 13. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol*. 2001;91:534-551.
 14. Smith HK, Plyley MJ, Rodgers CD, McKee NH. Expression of developmental myosin and morphological characteristics in adult rat skeletal muscle following exercise-induced injury. *Eur J Appl Physiol Occup Physiol*. 1999;80:84-91.
 15. Hortobagyi T, Hill JP, Houmard JA, et al. Adaptive responses to muscle lengthening and shortening in humans. *J Appl Physiol*, 1996;80:765-772.
 16. Hortobagyi T, Barrier J, Beard D, et al. Greater initial adaptations to submaximal muscle lengthening than maximal shortening. *J Appl Physiol*. 1996;81:1677-1682.
 17. LaStayo PC, Pierotti DJ. Eccentric ergometry: increases in locomotor muscle size and strength at low training intensities. *Am J Physiol Regul Integr Comp Physiol*. 2000; 278:1282-1288.
 18. LaStayo PC, Ewy GA, Pierotti DD, et al. The positive effects of negative work: increased muscle strength and decreased fall risk in a frail elderly population. *J Gerontol A Biol Sci Med Sci*. 2003;58:M419-424.
 19. Colliander EB, Tesch PA. Effects of eccentric and concentric muscle actions in resistance training. *Acta Physiol Scand*. 1990;140:31-39.
 20. Clarkson PM, Byrnes WC, McCormick KM, et al. Muscle soreness and serum creatine kinase activity following isometric, eccentric, and concentric exercise. *Int J Sports Med*, 1986;7:152-155.
 21. Ebbeling CB, Clarkson PM. Exercise-induced muscle damage and adaptation. *Sports Med*, 1989;7:207-234.
 22. Newham DJ. The consequences of eccentric contractions and their relationship to delayed onset muscle pain. *Eur J Appl Physiol Occup Physiol*. 1988;57:353-359.
 23. Newham DJ, McPhail G, Mills KR, Edwards RH. Ultrastructural changes after concentric and eccentric contractions of human muscle. *J Neurol Sci*. 1983;61:109-122.
 24. Brooks SV, Faulkner JA. Severity of contraction-induced injury is affected by velocity only during stretches of large strain. *J Appl Physiol*. 2001;91:661-666.
 25. Faulkner JA, Brooks SV, Opitck JA. Injury to skeletal muscle fibers during contractions: conditions of occurrence and prevention. *Phys Ther*. 1993;73:911-921.
 26. Vierck J, O'Reilly B, Hossner K, et al. Satellite cell regulation following myotrauma caused by resistance exercise. *Cell Biol Int*. 2000;24:263-272.
 27. Adams GR. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J Appl Physiol*. 2002;93:159-167.
 28. Barber M, Braid V, Glimore D, et al. IGF-1 levels, leg extensor power and physical performance after proximal femoral fracture. *Age Ageing*, 2003;32:678-680.
 29. Jennische E, Hansson HA. Regenerating skeletal muscle cells express insulin-like growth factor I. *Acta Physiol Scand*. 1987;130:327-332.
 30. Grounds MD. Reasons for the degeneration of ageing skeletal muscle: a central role for IGF-1 signalling. *Biogerontology*. 2002;3:19-24.
 31. Clarkson PM. Eccentric exercise and muscle damage. *Int J Sports Med*. 1997;18 Suppl 4:S314-317.
 32. Nosaka K, Clarkson PM. Muscle damage following repeated bouts of high force eccentric exercise. *Med Sci Sports Exerc*.1995;27:1263-1269.
 33. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther*. 2000;80:896-903.
 34. Nosaka K, Clarkson PM, Changes in indicators of inflammation after eccentric exercise of the elbow flexors. *Med Sci Sports Exerc*. 1996;28:953-961.
 35. Manfredi TG, Fielding RA, O'Reilly KP, et al. Plasma creatine kinase activity and exercise-induced muscle damage in older men. *Med Sci Sports Exerc*. 1991;23:1028-1034.
 36. Paddon-Jones D, Abernethy PJ. Acute adaptation to low volume eccentric exercise. *Med Sci Sports Exerc*. 2001;33:1213-1219.
 37. Evans WJ, Meridith CN, Cannon JG, et al. Metabolic changes following eccentric exercise in trained and untrained men. *J Appl Physiol*. 1986;61:1864-1868.
 38. Toft AD, Jensen LB, Bruunsgaard H, et al. Cytokine response to eccentric exercise in young and elderly humans. *Am J Physiol Cell Physiol*, 2002;283:C289-295.
 39. Smith LL, Anwar A, Fragen M, et al. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol*. 2000;82:61-67.
 40. Pedersen BK, Ostrowki K, Rohde T, Bruunsgaard H. The cytokine response to strenuous exercise. *Can J Physiol Pharmacol*. 1998;76:505-511.
 41. Kraemer WJ, Hakkinen K, Newton RU, et al. Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. *J Appl Physiol*. 1999;87:982-992.
 42. Tidball JG. Inflammatory cell response to acute muscle injury. *Med Sci Sports Exerc*. 1995;27:1022-1032.
 43. LaStayo PC, Woolf JM, Lewek MD, et al. Eccentric muscle contractions: their contribution to injury, prevention, rehabilitation, and sport. *J Orthop Sports Phys Ther*, 2003;33:557-571.
 44. Lindstedt SL, LaStayo PC, Reich TE. When active muscles lengthen: properties and consequences of eccentric contractions. *News Physiol Sci*. 2001;16:256-261.

45. Dibble LE, Hale T, Marcus RL, et al. The safety and feasibility of high-force eccentric resistance exercise in persons with Parkinson's disease. *Arch Phys Med Rehabil.* 2006;87:1280-1282.
46. Dibble LE, Hale TF, Marcus RL et al. High-intensity resistance training amplifies muscle hypertrophy and functional gains in persons with Parkinson's disease. *Mov Disord.* 2006;21:1444-1452.
47. Hortobagyi T. The positives of negatives: clinical implications of eccentric resistance exercise in old adults. *J Gerontol A Biol Sci Med Sci.* 2003;58:417-418.
48. Hortobagyi T, DeVita P. Favorable neuromuscular and cardiovascular responses to 7 days of exercise with an eccentric overload in elderly women. *J Gerontol A Biol Sci Med Sci.* 2000; 55:B401-410.
49. Singh MA, Ding W, Manfredi TJ, et al. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *Am J Physiol.* 1999;277:E135-143.
50. Parkhouse WS, Coupland DC, Li C, Vanderhoek KJ. IGF-1 bioavailability is increased by resistance training in older women with low bone mineral density. *Mech Ageing Dev.* 2000;113:75-83.
51. Berman S, Ferrari P, Bernard P, et al. Responses of total and free insulin-like growth factor-I and insulin-like growth factor binding protein-3 after resistance exercise and training in elderly subjects. *Acta Physiol Scand.* 1999;165:51-56.
52. Borst SE, Vincent KR, Lowenthal DT, Braith RW. Effects of resistance training on insulin-like growth factor and its binding proteins in men and women aged 60 to 85. *J Am Geriatr Soc.* 2002;50:884-888.
53. Nicklas BJ, Ryan AJ, Treuth MM, et al. Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55-70 years. *Int J Sports Med.* 1995;16:45-50.
54. Yan Z, Biggs RB, Booth FW. Insulin-like growth factor immunoreactivity increases in muscle after acute eccentric contractions. *J Appl Physiol.* 1993;74:410-414.
55. Hameed M, Orrell RW, Cobbold M, et al. Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise. *J Physiol.* 2003;547:247-254.
56. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med.* 1990;323:1-6.
57. Teale JD, Marks V. The measurement of insulin-like growth factor I: clinical applications and significance. *Ann Clin Biochem.* 1986;23:413-424.
58. Liu JL, Yakar S, LeRoith D. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. *Proc Soc Exp Biol Med.* 2000;223:344-351.
59. Adams GR, Haddad F. The relationships among IGF-1, DNA content, and protein accumulation during skeletal muscle hypertrophy. *J Appl Physiol.* 1996;81:2509-2516.
60. Adams GR, McCue SA, Localized infusion of IGF-I results in skeletal muscle hypertrophy in rats. *J Appl Physiol.* 1998;84:1716-1722.

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Baylor University.....	Inside Front Cover
Kneebourne	127
St. Catherines	113
Sprint Aquatics.....	120