ABSTRACT

Title of Document: INSULIN-LIKE GROWTH FACTOR 1 GENOTYPE AND MUSCLE POWER RESPONSE TO STRENGTH TRAINING IN OLDER MEN AND WOMEN.

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Purpose: To determine if the *IGF1* $(CA)_{19}$ repeat polymorphism influences muscle power at baseline and in response to strength training (ST) in older adults.

Methods: Knee extensor (KE) peak power (PP) was measured at 50, 60, and 70% of 1 RM strength before and after 10 wks of unilateral KE ST in older adults, aged 50-85 yr., to determine the changes in absolute and relative PP with ST. Subjects (N = 114) were genotyped for the *IGF1* CA repeat polymorphism and grouped as homozygous for the 192 allele, heterozygous, or non-carriers of the 192 allele. However, sample sizes varied substantially among the various dependent variables. Differences in baseline PP and changes with ST among genotype groups were determined using ANCOVA (covariates include: age, sex, baseline fat-free mass).

Results: The 192 homozygotes had significantly lower baseline PP at 50%, 60%, and 70% of 1-RM strength than the non-carriers when age, sex and baseline fat-free mass was covaried. This same relationship was observed when the highest PP within these

ranges was compared. Both absolute and relative PP increased significantly with ST in all genotype groups as expected, but there were no significant relationships between *IGF1* genotype and any of the PP changes. **Conclusion:** Despite a significant relationship between *IGF1* genotype and knee extensor peak power at baseline, *IGF1* genotype does not appear to influence changes in knee extension peak power with ST.

INSULIN–LIKE GROWTH FACTOR 1 GENOTYPE AND MUSCLE POWER RESPONSE TO STRENGTH TRAINING IN OLDER MEN AND WOMEN

By

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INTRODUCTION

Sarcopenia is the loss of muscle mass with age and is associated with declines in muscle strength (62) muscle power (220,148,179) and losses of functional abilities (228,296). Muscle power, the product of force generation and the velocity of muscle contraction, is a particularly important component of sarcopenia because its age-related deterioration rate is greater than losses in muscle strength or muscle mass (148,179,260) and it is believed to be more closely associated with declines in functional abilities than muscle strength in elderly population (171,217). For example, leg power explains a larger portion of the variation within physical function performance than does leg strength in older men and women (22,119).

Several types of interventions have been proposed for the prevention and delay of the adverse consequences of sarcopenia, but the combined efficacy and safety qualities of strength training (ST) make it the intervention of choice for older adults (122,238,121). ST increases muscle power in older adults even when moderate-velocity protocols are used (134,261,75). However, muscle response to ST is highly variable, even among those with similar physical characteristics undergoing equivalent training programs (58,126,125,33).

These large inter-individual differences, along with the high heritability values for muscle power (273,35), suggests that genetic factors may be influential. Also, power is influenced by both maximal force production (strength) and muscle mass, both of which are highly heritable phenotypes (123). In addition, the adaptation in the muscle with response to ST has been shown to have genetic correlations (60,272).

Despite the importance of muscle power as a major component of sarcopenia, little information is available on the influence of specific gene polymorphisms on muscle power at baseline or in response to ST in older adults (59).

The contribution of insulin-like growth factor I (IGF-I) in the modulation of muscle mass and function across the entire life span has been well established (86,27,192). Circulating levels of IGF-I decline with age, and is related to sarcopenia (95,279). Low plasma IGF-I levels are associated with slow walking speed and self-reported difficulty in mobility tasks, suggesting a role of IGF-I in disability and frailty in the elderly (37). The expression of IGF-I within individual muscle fibers is correlated with muscle hypertrophy resulting from mechanical overload (212,308). Moreover, over expression of IGF-I in skeletal muscle elicits muscle fiber hypertrophy (47,192) and IGF-I mRNA levels are associated with muscle hypertrophy (307,49). Some recent studies in transgenic mice have also related the over expression of IGF-I in skeletal muscle to prevention of age-related decreases in intracellular calcium and specific force in a muscle (89,298). In addition, IGF-I is a potent trophic factor for motor neurons (40) and over expression of IGF-I in skeletal muscle prevents denervation of fast muscle fibers in aged mice (178). Though only few studies have investigated the association between IGF-I and muscle power in humans, the findings of one such study indicated that in healthy elderly women, lower values for quadriceps muscle power and optimal shortening velocity are related to lower circulating levels of IGF-I (149). In another study, IGF-I was a significant predictor of muscle power in older adults, even after adjusting for potential confounders, such as age, sex and body mass index (12). Though several studies

have shown ST to be effective in increasing muscle IGF-I mRNA and protein levels, even in the elderly (101,258) , we are unaware of any studies showing these increases are associated with muscle power adaptations with ST.

Although numerous factors can influence blood or tissue levels of IGF-I, a large percentage of the variability appears to have a genetic basis (116,107). Studies have implicated an area near the *IGF1* gene locus with influencing baseline fat free mass (FFM) and FFM changes with training, thus making it a strong candidate gene for muscle phenotypes (42,267). A cytosine-adenine $(CA)_{19}$ dinucleotide repeat polymorphism (192 repeat allele) in the promoter region of the insulin-like growth factor 1 (*IGF1)* gene is associated with blood levels of the IGF-I protein (229,183,288,236). Several studies have also associated this repeat polymorphism with functional properties and phenotypes linked to IGF-I protein (289,288,236,246,231,286). Two recent studies have reported that the development of muscular strength in response to a ST program is influenced by this *IGF1* dinucleotide repeat polymorphism located in the promoter region (104,147). The exact functionality of this polymorphism is not known, however, the results of the above studies suggest that the polymorphism may serve at least as a candidate marker for muscle phenotypes associated with IGF-I. Presently, there are no studies that have investigated the relationship between this repeat polymorphism in the *IGF1* gene and muscle power. Knowledge of this relationship may have important implications for understanding the impact of genetics on muscle power.

Therefore, the purpose of the study is to determine whether *IGF1* genotype in the promoter region is associated with skeletal muscle power at baseline and in response

to ST in older adults. Because of the associations described above between the repeat polymorphism in the *IGF1* gene and expression of IGF-I protein in muscle and between IGF-I protein and skeletal muscle properties, we hypothesize that the repeat polymorphism in the *IGF1* gene is related to skeletal muscle power at baseline and in response to ST. Due to the substantial loss in muscle power with advancing age and the close association between muscle power and performance of functional abilities in the elderly, this association in older adults could have important clinical significance.

METHODS

Participants

One hundred and fourteen relatively healthy, sedentary, predominantly Caucasian and African-American men and women volunteers between the ages of 50 and 85 were recruited in this study. The data for some of these subjects have been previously used by two other studies from our group that have explored the relationship between *IGF1* genotype and strength training response of other muscle phenotypes (147,104). All subjects underwent a phone-screening interview, received medical clearance from their primary care physician and completed a detailed medical history prior to participating in this study. All subjects were nonsmokers, free of significant cardiovascular, metabolic, or musculoskeletal disorders that would affect their ability to safely perform heavy resistance exercise. Subjects who were already taking medications for at least three weeks prior to the start of the study were permitted into the study as long as they did not change medications or dosages at any time throughout the study. After all methods and procedures were explained, subjects read and signed a written consent form, approved by the Institutional Review Board of the University of Maryland, College Park. All subjects were continually reminded throughout the study not to alter their regular physical activity levels or dietary habits for the duration of the investigation, and body weight were measured weekly throughout the study to help confirm compliance to maintaining a stable diet. All subject information was kept confidential.

Research Design

This retrospective gene association study with a longitudinal ST intervention utilized a pre and post non random design. The *IGF1* genotype groups serve as the independent variable, whereas KE PP assessed at baseline and the change in KE PP with ST serves as the dependent variables to test the hypotheses.

Genotyping

Blood was drawn from the antecubital vein of the dominant arm, after at least twelve hours of fasting. Genomic DNA was extracted from peripheral lymphocytes. The CA microsatellite of *IGF1* was amplified using polymerase chain reaction (PCR) using fluorescence tagged primers. Previously published PCR primers flanking the CA polymorphism were used (236).The ABI 3100 DNA sequencer (PE Applied Biosystems) and AB Genescan/Genotyper 2.5 software program (PE Applied Biosystems) were used to determine the genotype of the CA repeat microsatellite in the promoter region of the *IGF1* gene. Genotype assignment was based on the method described by Rosen et al (236) (e.g., 19 CA repeats = 192 bp), in which these authors found the 192 allele to be the most common and thus compared it with the other alleles for this microsatellite (236). Direct sequencing was used to confirm the accuracy of all genotyping methods.

Body Composition Assessment

Body composition was determined by dual-energy x-ray absorptiometry (DXA) using the fan-beam technology (model QDR 4500A, Hologic, Waltham, MA). A total body scan was performed at baseline and again after the ST program using standardized procedures for patient positioning and the QDR software. Total body

FFM, fat mass, and % fat were analyzed using Hologic version 8.21 software for tissue area assessment. Total body FFM was defined as lean soft tissue mass plus total body bone mineral content (BMC). The coefficients of variation (CV) for all DXA measures of body composition were calculated from repeated scans of 10 subjects who were scanned three consecutive times with repositioning. The scanner was calibrated daily against a spine calibration block and step phantom block supplied by the manufacturer. In addition, a whole body phantom was scanned weekly to assess machine drift over time.

Body weight was measured to the nearest 0.01 kg with subjects dressed in medical scrubs, and height was measured to the nearest 0.1 cm using a stadiometer (Harpenden, Holtain, Wales, UK). Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Muscular Strength

One-repetition maximum (1- RM) strength test. The 1-RM strength test was performed for both legs on a knee extension (KE) exercise at baseline and after 10-week of unilateral (one-legged) KE ST program, using an air-powered resistance machine (Keiser A-300 Leg Extension machine, Keiser Sports/Health Equip. Co., Inc., Fresno, CA). This exercise was chosen because it can be easily tested in a standardized way using objective criteria. Before the regular ST program, 1- RM testing, and power testing were performed, subjects underwent at least two familiarization sessions in which the participants completed the training program exercises with little or no resistance and were instructed on proper warm-up, stretching and exercise techniques. These low-resistance training sessions were

conducted in order to familiarize the subjects with the equipment, to help control for the large 1- RM strength gains that commonly result from skill (motor learning) acquisition during the initial stages of training, and to help prevent injuries and reduce muscle soreness following the strength testing protocol. When appropriate, straps and/or belts were used to stabilize the subject so that recruitment of outside muscle groups was minimized. Arms were placed either across their chest or on thighs during exercise, but positioning was consistent from pre- to post testing within subjects. The 1- RM was achieved by gradually increasing the resistance from an estimated sub-maximal load after each successful exercise repetition until the maximal load was obtained. A light system was used to indicate a successful attempt when the knee was extended to the full ROM. Approximately the same number of trials (6-8) and the same rest periods between trials (~ 1 min) were used to reach the 1- RM after training as before training. Subjects rating of perceived exertion and pain/discomfort were monitored and recorded throughout the test. The same investigator conducted strength tests for each subject both before and after training and standardized procedures with consistency of seat adjustment, body position, and level of vocal encouragement were used.

Muscle Volume

Computed Tomography (CT). To quantify quadriceps muscle volume (MV), CT imaging of the trained and untrained thighs was performed (GE Lightspeed Qxi, General Electric, Milwaukee) at baseline and during the last weeks of the 10-week unilateral ST program. Axial sections of both thighs were obtained starting at the most distal point of the ischial tuberosity down to the most proximal part of the

patella while subjects were in a supine position. Section thickness was fixed at 10 mm, with 40 mm separating each section, based on previous work in our laboratory by Tracy et al (281). Quadriceps MV was estimated based on using a 4 cm interval between the center of each section. Each CT image was obtained at 120 kVp with the scanning time set of 1 s at 40 mA. A 48-cm field of view and a 512 X 512 matrix was used to obtain a pixel resolution of 0.94 mm. Two technicians analyzed images for each subject using Medical Image Processing, Analysis, and Visualization (MIPAV) software (NIH, Bethesda). Briefly, for each axial section, the cross-sectional area (CSA) of the quadriceps muscle group was manually outlined as a region of interest. The quadriceps CSA was manually outlined in every 10 mm axial image from the first section closest to the superior border of the patella to a point where the quadriceps muscle group was no longer reliably distinguishable from the adductor and hip flexor groups. The same number of sections proximal from the patella was measured for a particular subject before and after training, to ensure within subject measurement replication. Investigators were blinded to subject identification, date of scan, and training status, for both baseline and after training analysis. Repeated measurement CV was calculated for each investigator based on repeated measures of selected axial sections of one subject on two separate days. Final MV was calculated using the truncated cone formula as reported by Tracy et al (281) and described by Ross et al (237).

Peak Muscle Power

Determination of KE PP was performed on a customized Keiser pneumatic resistance knee extension (K410) machine (Keiser Sports/Health Equip. Co., Inc.,

Fresno, CA), specifically designed for muscle power assessment. The K410 machine is equipped with load cell force transducers and position sensors to detect rotary motion at the joint. Additionally, a computer program (A430 version 1.6.0.19 (2003), Keiser Sports/Health Equip. Co., Inc., Fresno, CA) was used to measure muscle power in Watts. The Keiser machine measures maximal movement velocity and force production to calculate muscle power in watts, using a specialized timing device and load cell.

Prior to testing, seated blood pressure was measured after five minutes of rest, and then a one-minute warm-up was performed on a stationary cycle ergometer. Subjects were then positioned on the K410 with the medial condyle aligned with the axis of rotation of the machine arm. Subjects were instructed to cross their arms across their chest, and a seat belt attached to the machine was securely fastened around the waist to help isolate the knee extensor muscle group. Subjects were instructed to perform a knee extension with each leg unilaterally at a resistance of ~ 30% of their measured 1- RM and at ~ 50% of their maximal velocity, as a warm-up trial. Following a 30 s rest period, subjects performed three power tests on each leg alternating between right and left at 50%, 60%, and 70% of their 1- RM, with a 30 s rest period between each of the three trials and 2 min rest periods between each increase in resistance. The tester offered standardized oral encouragement to each subject to extend his or her knee as quickly and forcefully as possible during each trial. The highest peak power value of the three trials for each % of 1- RM was selected. The entire procedure was repeated 48-72 h later and the higher of the two values was used as baseline peak power, as this value would better approximate peak

power. This test was repeated during the last week of the 10-week unilateral ST program for the post training test. During this latter test, an attempt was made to find a load that could be replicated from baseline testing that represented 50% or 60% of the post training 1- RM for testing at the same absolute load. When a replicable load was not found that fell at one of these relative loads (i.e., 50% or 60% of the post training 1- RM), the load that was used at 50% of the baseline 1- RM value was used for the post training same absolute load (regardless of the % of post training 1- RM that the load represents) during the post training test. The power machine was calibrated daily against a standardized weight supplied by the manufacturer. Muscle power testing was shown to be both reliable and valid in a previous study using similar equipment, with an intra-class correlation coefficient of 0.91 (34).

Training Program

The training program consisted of unilateral (one-legged) training of the knee extensors of the right leg, three times per week, for ~ 10 weeks. Training was performed on a Keiser A-300 air powered leg extension machine. This machine allows for ease of changing the resistance without interrupting the cadence of the exercise. The untrained control leg was kept in a relaxed position throughout the training program. Subjects performed a warm-up on a bicycle ergometer for approximately two minutes prior to each training session. Following the two familiarization training sessions previously described, the training consisted of five sets of knee extension exercise for those < 75 yrs of age and four sets for those ≥ 75 yrs of age. We did not have those ≥ 75 perform the last set because of our concern that performing 50 repetitions at near maximal effort for this age group might cause

overtraining, which has been shown to result in a reduction in strength gains with training (207). The first set was considered warm-up and consisted of five repetitions at 50% of the 1- RM strength value. The second set consisted of five repetitions at the current 5 -RM value, which was initially estimated based on our previous data showing that it corresponds to ~ 85% of 1- RM in most people. Adjustments were made as needed during each training session so that the resistance used resulted in failure to complete a 6^{th} repetition. The 5 -RM value was increased continually throughout the training program to reflect increases in strength levels. The first four or five repetitions of the third set were performed at the current 5- RM value, then the resistance was lowered just enough to complete one or two more repetitions before reaching muscular fatigue. This process was repeated until a total of 10 repetitions were completed. This same procedure was used in the fourth and fifth sets, but the total number of repetitions was increased in each set to 15 and 20 reps, respectively. This procedure allowed subjects to use near maximal effort on every repetition while maintaining a relatively high training volume. The second, third, fourth, and fifth sets were preceded by rest periods lasting 30, 90, 150, and 180 seconds, respectively. A red light indicator was visible to the participant and flashed only when the full ROM was reached. The shortening phase of the exercise (often called concentric phase) was performed in approximately two seconds, and the lengthening phase (often called eccentric phase) lasted approximately three seconds. A seat belt was worn throughout the exercise session and subjects placed their arms across their chest during exercise in order to minimize involvement of assisting muscles. Subjects performed supervised stretching of the knee extensors and hip flexors following each

training session. Trained research assistants carefully monitored the work-outs of each participant for every training session during the ~10 weeks of training. They adjusted the resistance accordingly within the set and for the following training session in order to ensure each repetition was performed using the proper resistance and form through the full ROM.

Statistical Analysis

All statistical analyses as described below were performed using SAS software (SAS version 9.1, SAS institute, Inc., Cary NC). The significance of the statistical model was set at $P < 0.05$ and data comparisons are expressed as means +/- SE. To examine the effect of the promoter genotype on skeletal muscle power at baseline and in response to ST, an analysis of covariance was used for each dependent variable to test for differences among means. The three levels of the predefined groupings of genotype at the *IGF1* promoter locus were defined as the fixed effect. To reduce error variance and increase precision, age, gender and baseline FFM were used as covariates for the analysis. Race and usage of ACE inhibitors, diuretics, anti-inflammatory medications, and hormone replacement therapy (HRT) did not reach significance as covariates and were therefore not included in the final model. To determine whether the data for the Caucasian and African-American populations could be pooled for the potential influence of race on the *IGF1* genotype and muscle power relationship at baseline and in response to ST, analysis was done with and without including race as a covariate and no differences in results were observed. For this reason, data from both race groups was combined for all other genotype analyses to improve statistical power.

To explain percent variability explained by genotype, the proportion of the variance explained by the 192 CA dinucleotide repeat polymorphism , the R^2 of the full model with *IGF1* genotype and all covariates was compared to that of the constrained model without *IGF1* genotype in the model.

Statistical Power. Post-hoc power analysis was done to determine the power level given the pre-set sample size using all data from the present study, with α. Set at 0.05. Statistical power was ≥ 0.8 for all baseline muscle power comparisons between the 192 homozygotes and non-carriers of the 192 allele. The statistical power to detect baseline muscle power differences between 192 homozygotes and 192 heterozygotes; 192 heterozygotes and non-carriers of the 192 allele was < 0.5 and < 0.25 for changes in muscle power with ST. Based on this analysis, a sample size of >500 would be required to achieve a statistical power of 0.8 to detect differences among genotype groups for changes in muscle power with ST. This value would increase substantially if attrition and ethnicity were considered.

RESULTS

Subject characteristics and muscle properties at baseline and after ST for men (n = 52) and women (n = 62) are shown in Table 1. Strength increased significantly in the trained leg in men (~ 25.9 %) and in women (~29.3 %, both $P < 0.001$) with ST, irrespective of *IGF1* genotype. These increases are likely reduced by our familiarization procedures performed prior to baseline strength testing and designed to control for motor learning effects (see methods for explanation). Muscle volume (MV) also significantly increased in both men (~ 8.8 %) and women (~ 8.1 %; both $P < 0.001$). There were no significant changes in BMI, body mass , % body fat, or FFM in either men or women with ST. Table 2 reveals no significant differences in age, height, body mass, BMI, , % body fat or FFM at baseline or in response to training among the three *IGF1* promoter genotype groups.

As shown in Table 3, there was a significant increase (31 ± 6 W; 9 %; $P < 0.001$) in knee extensor absolute PP (i.e., PP at the same absolute resistance at both baseline and after ST) in all subjects with ST, irrespective of *IGF1* genotype. Relative PP (i.e., PP at 50%, 60% and 70% of baseline 1- RM and 50%, 60% and 70% of the improved 1- RM after ST) also significantly increased (20 ± 5; 6 %; P < 0.001, 15 ± 6; 4 %; P < 0.05, & 13 ± 6; 4 %; P < 0.05, respectively) in all subjects, irrespective of genotype. Finally, in all genotype groups, the overall highest relative peak power, irrespective of the % of 1- RM, also showed a significant increase (22 ± 4; 6%; P < 0.001). In the current sample population, the overall highest relative peak power for most participants (i.e., 58 % of the participants) was obtained at 50% of the 1- RM

value. The only variables that changed significantly in the untrained leg in all subjects was 1- RM strength ($P < 0.001$) and this was likely due to the cross-education effect. The changes in 1- RM, muscle volume, absolute PP and relative PP in the trained leg were significantly different than those of the untrained leg in all subjects (all at least $P < 0.05$).

Genotype results. Due to the longitudnal design of the investigation and multiple variables examined within each genotype group, many of the measures have missing data points. The minimum number of subjects for any of the main variables with ST is 18, 24 and 15 for the 192 homozygotes, 192 heterozygotes, and all other genotype groups, respectively. As shown in table 4, genotype distributions for the *IGF1* genotype groups were 36 (32%), 55 (48%), and 23 (20%) for the 192 homozygotes, 192 heterozygotes and "all other genotypes" group, respectively, and were comparable to those reported previously (236,288). The 192 allele was however, observed more frequently in the Caucasians than African-Americans, who had a higher frequency of the non-192 allele, as reported previously (140,246).

Table 5a shows the baseline differences in peak power in all subjects by *IGF1* genotype. The 192 homozygotes had significantly lower baseline PP at 50%, 60%, and 70% of 1 RM strength (58 W, 64 W, & 58 W, respectively) than the non-carriers ($P < 0.05$) when age, sex and baseline FFM were covaried. This same relationship was observed when the highest PP within these ranges was compared. Partial R^2 analysis indicated that the *IGF-1* genotype explained 2.0% - 2.3% of the variance in baseline PP. As sex was a significant covariate in the model for the baseline peak power values shown in table 5a, separate analyses were performed for

baseline peak power values of each sex group by *IGF1*genotype. Table 5b and Table 5c show the differences in baseline PP in women and men respectively by *IGF1* genotype. As shown in Table 5b, the 192 homozygote women had significantly lower baseline PP at 50% and 70% of 1 RM strength (60 W & 59 W respectively) than the non-carriers ($P < 0.05$) when age and baseline FFM were covaried. In women, the overall highest relative PP was also significantly lower in 192 homozygotes and 192 heterozygotes by 69 W & 52 W, respectively, than the non-carriers ($P < 0.05$). There were no baseline differences in peak power by *IGF1* genotype in men as shown in Table 5c .

Table 6 shows the differences in change in peak power with ST by *IGF1* genotype in all subjects. The change score is calculated as the difference between the muscle power change with training in the trained leg and that of the control leg during this same time period. Absolute and relative peak power change scores did not differ significantly among the *IGF1* promoter genotype groups ($P > 0.05$), when covarying for age, sex and baseline FFM.

As shown in Tables 7a, 7b, 7c and 7d, an exploratory sub-analysis revealed some race specific differences in *IGF1* genotype influence on both baseline and change in peak power with ST, when covarying for age, sex and baseline FFM. No significant differences were observed in baseline or change in peak power with ST among the *IGF1* genotype groups in Caucasians, whereas, African-American 192 homozygotes had significantly lower PP than non-carriers at baseline 70% of 1-RM and at the overall highest relative baseline PP (both $P < 0.05$). The African-American 192 homozygotes also had significantly higher absolute (at the same absolute resistance at

both baseline and after ST) and relative peak power (60% of 1-RM at baseline and 60% of the improved 1- RM after ST) change with ST than the non-carriers ($P < 0.05$).

DISCUSSION

To our knowledge, this is the first study to examine the influence of *IGF1* genotype on skeletal muscle power at baseline and in response to ST in older adults. Although the results support our hypothesis that *IGF1* genotype influences knee extensor PP at baseline, it appears to only account for a small portion of the variation in muscle power (~ 2%). Contrary to our expectations, the data do not support our hypothesis of a significant influence of *IGF1* genotype on change in knee extensor PP with ST. This latter finding, however, does not completely rule out *IGF1* as an important gene or the *IGF1* $(CA)_{19}$ repeat polymorphism as an important gene locus for influencing muscle power response to ST. Nevertheless, it does appear that other gene loci should be explored in future investigations to better determine the role of gene polymorphisms in explaining variability in muscle power response to ST.

The common *IGF1* $(CA)_{19}$ microsatellite polymorphism may alter transcription through its regulatory elements (175,301), and has been associated with decreased circulating levels of the IGF-I protein in some (80,236,229) but not all studies (4,56,132). This polymorphism is also associated with functional properties and phenotypes linked to the IGF-I protein (236,231,246,286,288,289). Despite the known effects of IGF-I on muscle biology, we could only find two reports that have examined this polymorphism in relation to skeletal muscle phenotypes. Both of these studies reported no significant differences in baseline muscle strength, muscle volume or muscle quality (MQ) among *IGF1 CA* repeat genotype groups (147,104). However, Kostek et al (147) found a significant influence of the *IGF1* genotype on muscle strength response to strength training. These findings were further extended

by Hand et al (104) who observed a significant *IGF1* main effect, as well as a significant gene by gene interaction effect for *IGF1* and calcineurin B (*PPP3R1)* for change in strength and MQ with ST. The results of the present study add to these two studies, which used some of the same subjects who were used in this investigation, by showing a significant association of this *IGF1* polymorphism with baseline knee extensor PP, but not with change in knee extensor PP with ST. Until corroborative findings from independent cohorts support our baseline findings, it may be premature to speculate on potential mechanism. Nevertheless, one possibility for explaining such a link might relate to the trophic effects of IGF-I on neuronal and muscular tissues, given that muscle power is associated with both muscular and neurological factors (111).

Our results show that the non-carriers of the 192 allele had the highest PP values, followed by the 192 heterozygotes and 192 homozygotes, respectively, but only the women were significantly higher. Our finding of a sex-specific association between *IGF1* genotype and knee extensor PP is similar to that reported by Kostka et al (149), who showed a positive correlation between plasma IGF-I levels and quadriceps power in women, whereas, no such correlation was observed in men. They speculated that cortisol and testosterone levels may be better predictors of muscle function in men than IGF-I levels. While it is possible that the physiologically low concentration of testosterone in women may induce compensatory stimulation of the growth hormone/IGF-I axis in response to an increase in muscle loading, it is far beyond the scope of this study to determine potential mechanisms for this sex-specific finding. Nevertheless, our observed sex difference in the associated influence of

IGF1 genotype on muscle power warrants further exploration. Given that elderly women have 20-80% lower muscle power than men (260,16,64), which predisposes them to a greater and earlier risk of falls and loss of independence than men (268,201), muscle power is an important issue for health status and functional abilities in older women. Moreover, the relative power assessed may have additional implications. For example, Cuoco et al. (48) demonstrated that lower extremity power at 40% of 1 RM explained a greater proportion of the variance in habitual gait velocity than did muscle power at 70% of 1 RM. In this context, we found a significant association between *IGF1* genotype and PP at a lower relative intensity (50% of 1 RM). The positive association between *IGF1*genotype and PP at higher relative intensities (e.g., 70% of 1 RM), may also have important functional implications for other activities of daily living, such as getting in and out of a chair, which require a higher percentage of maximal force production (303,306).

Although there was a significant association between *IGF1* genotype and baseline knee extensor power, no such association was observed with knee extensor power gain after training. This is in contrast to the positive associations reported in previous studies between *IGF1* genotype and muscle strength response to ST (147,104). Based on the principle of specificity, it is not surprising that we observed a greater increase in 1-RM strength than power, given our moderate velocity, heavy resistance training protocol. However, it is conceivable that this could at least partially explain the significant associated influence of *IGF1* genotype on strength response to ST previously reported. The more subtle changes in power compared to strength may have made it more unlikely to detect a statistically significant genotype association

than strength, even if a true relationship existed. In addition due to the longitudinal design of the investigation, the small sample size for change in muscle power in each genotype group resulted in low statistical power and a high possibility of type 2 error. Thus, the inconclusive results in influence of *IGF1* genotype on muscle power response to ST may be due to lack of statistical power and future studies with large sample size should confirm this finding.

Previous studies have reported significant differences in strength, muscle volume and lower extremity performance among racial/ethnic groups (222,64,197,296). Although a complete explanation for these differences has not been identified it is conceivable that racial heterogeneity in circulating IGF-I levels could offer at least a partial explanation. Racial differences in IGF-I levels is associated with risk of diabetes, cardiovascular disease, and cancer in certain race groups (250,23). Although the findings of racial differences for the influence of *IGF1* genotype on muscle phenotypes in the current study are based on insufficient sample sizes, they may offer support to the need for future studies to further explore the role of the IGF-I axis in explaining racial/ethnic differences in muscle phenotypes. In this context, it is possible that racial/ethnic differences in serum IGF-I could occur because of genetic differences in IGF-I regulation among different race/ethnic groups, as a large percentage of variability in serum IGF-I levels has a genetic basis (107,116). This is further supported by our own data and the reports of previous investigations showing an ethnic variation in the frequency of the 192 allele (56,140), which has been associated with serum IGF-I levels. To address the issue of racial influences on the genotype/phenotype relationship between IGF-I and muscle structure or function at

baseline or in response to exercise training, future studies will need to use large sample size with similar numbers of subjects from different racial and genotype groups, controlling for the possible divergent effects this polymorphism might have among different racial/ethnic backgrounds (118).

The use of the untrained leg adds a unique design that controls for drift in values due to common variations in methodology, biology, season of the year, genetic differences between groups, or differences in attention between experimental and control groups. This in combination with our data showing no cross-education effect of muscle power in the untrained leg with ST of the trained leg minimizes the level of variance due to experimental error and better isolates the independent effects of ST and influences of gene variations. Furthermore, our measure of PP as the highest power value attained during a single trial, unlike previous investigations reporting PP as the highest average power obtained during multiple trials of a power test (66,76,134,127), might be a more accurate measure of the explosive capacity of the trained musculature. Additionally, our measure of PP might be more functionally relevant to events such as catching oneself from a fall or quickly correcting a loss of balance, because these actions would likely be limited by the ability to instantaneously maximize both strength and speed of movement (91,304). More specifically, since knee weakness is strongly correlated to the occurrences of falls and disability in the elderly (96), quadriceps power measured in the current study may be considered one of the most important determinants of functional independence in older adults.

Despite the value of our design for the internal validity of the study, there are several limitations in the current investigation. Although the untrained leg helps minimize the error variance in the dependent variables of interest, the small sample size in each of the genotype groups and the lack of an independent cohort for comparison still poses a major limitation for genotype association studies. Another limitation is our moderate velocity training protocol (~ 2 seconds during the shortening phase and (~ 3 seconds during the lengthening phase). A faster velocity training program would likely optimize gains in power (76). We chose this ST protocol for its safety and effectiveness for improving muscle mass, strength, and muscle quality, as well as power (58,126,280,157), all key components of sarcopenia. The relatively large age range of subjects (50-85 yrs) is also a limitation. It is possible that the youngest subjects in the study may have slightly different training responses than the older ones. We attempted to control for this statistically by covarying for age, but an experimental control of narrowing the age range would have likely provided a better control for this. Moreover, the exact functional role for this *IGF1* polymorphism cannot be determined from this study. It is possible that the length of the polymorphism could be affecting expression levels or that this polymorphism is in linkage disequilibrium with a functional polymorphism that affects phenotypes related to *IGF1* expression. As recommended in previous studies, to address the functionality of this polymorphism *in-vivo* in humans, *IGF1* muscle expression data and IGF-I cellular mediators though muscle biopsy samples would be needed along with a method of grouping that could account for heterozygotes who carried one copy longer and one copy shorter than 19 repeats (147). Alternatively, a

cell culture system could be used to address this *in-vitro*. Finally, this investigation shows the relationship between only one polymorphism in only one gene at only one locus. However, muscle power is a complex phenotype, which is probably influenced by multiple genetic pathways and environmental influences. Performing this type of study, however, would require an extremely large sample size, likely to require multiple training cites.

Therefore, any future studies that address the question of genetic influences on muscle power response to ST will not only need to accommodate the limitations of this current study, but will also need to consider PP assessments in other movements experienced in common activities of daily living by older adults, such as upper leg extension used in the leg press exercise. Future studies could provide more information on the functionality of *IGF1* and other gene polymorphisms by measuring mRNA and/or protein levels of IGF-I in muscle samples. It may also be useful to study this and other IGF pathway gene polymorphisms as they relate to contraction velocity to get useful insights into potential mechanisms for genetic predispositions for decline in muscle power and function. This recommendation is based on the fact that deficits in movement velocity have been reported as the primary cause of age-related power losses, especially in older women (41,55) and have significant correlations with functional performance measures such as 6-m walking speed and chair and stair-climb time (46). Studies analyzing the association between this polymorphism and functional abilities in elderly populations would also be useful to make any recommendations for genetic susceptibility to sarcopenia based on this genotype. Additionally, future haplotype and gene x gene interaction studies are

needed and should be conducted in various ethnic backgrounds to explain a greater proportion of the variance of these complex phenotypes.

In summary, the present study is the first to demonstrate a significant association between *IGF1* genotype and muscle power in older adults. When confirmed and combined with those from larger cohorts, possibly targeting other sites, the results from this study could help contribute to a better understanding of the role of genetics in decline in muscle power with aging. This information could then eventually help to develop better screening procedures for the prevention and treatment of sarcopenia. However, the application of this information to this level of practical use will have to await much further study.

Table 1. Physical characteristics at baseline and after strength training (ST) in men and women.

	Men n= 52[1]		Women n=62[2]	
	Baseline	After ST	Baseline	After ST
Age (yr)	65 (8)	_ _	65 (9)	_ _
Height (cm)	174 (6.6)	_ _	162 (6.2)	_ _
Weight (kg)	85.3 (12.7)	85.6 (12.7)	73.8 (14.7)	73.8 (15.4)
BMI (kg/m^2)	28.1 (3.6)	28.2 (3.6)	28.2 (5.7)	28.2 (5.9)
Body Fat (%)	27.7 (5.1)	27.6 (4.7)	39.1 (6.1)	38.8 (6.0)
Fat-Free Mass (kg)	61.3 (7.6)	61.6 (7.3)	44.0 (5.6)	44.2 (5.9)
1-RM (kg)	32 (8.3)	40.3 (9.5)*	17.7 (5.6)	22.9 (6.2)*
Muscle Volume (cm^3)	1759 (276)	1914 (313)*	1153 (228)	1247 (232)*

Values are means (SD). Data presented are for all subjects with baseline and after ST measurements.
BMI = body mass index; 1-RM = knee extension one-repetition maximum; kg = kilograms.

[1]There were 49 subjects for weight, BMI, FFM & body fat %, 51 for muscle volume, 52 for 1-RM that had both baseline and after ST values.

[2]There were 60 subjects for body fat %, 61 for muscle volume & FFM, 62 for weight, BMI & 1-RM that had both baseline and after ST values.

[3]Muscle volume of the knee extensors.

*Significantly different than baseline ($P < 0.001$).

Table 2. Physical characteristics for all subjects by *IGFI* genotype

	192 Homozygotes		192 Heterozygotes		All other Genotypes	
	Baseline	After ST	Baseline	After ST	Baseline	After ST
Age (yr)	63 ± 1 (36)	_ _	66 ± 1 (55)	_ _	64 ± 2 (23)	_ _
Height (cm)	168.3 ± 1.5 (36)	_ _	165.9 ± 1.2 (55)	_ _	169.9 ± 1.8 (23)	_ _
Weight (kg)	79.2 ± 2.5 (35)	79.1 ± 2.6 (35)	78.5 ± 2.1 (53)	78.7 ± 2.1 (53)	79.3 ± 3.1 (23)	79.5 ± 3.2 (23)
BMI (kg/m^2)	28.0 ± 1.0 (35)	28.0 ± 1.0 (35)	28.5 ± 1.0 (53)	28.6 ± 1.0 (53)	27.5 ± 1.0 (23)	27.5 ± 1.0 (23)
Body Fat (%)	34.3 ± 1.4 (35)	34.1 ± 1.3 (35)	34.5 ± 1.1 (53)	34.3 ± 1.1 (53)	32.3 ± 1.8 (21)	31.7 ± 1.7 (21)
Fat-Free Mass (kg)	51.8 ± 1.8 (35)	51.8 ± 1.9 (35)	51.2 ± 1.5 (53)	51.5 ± 1.5 (53)	52.8 ± 2.3 (22)	53.4 ± 2.3 (22)
Male/Female, *n*	16/20	_ _	25/31	_ _	11/12	_ _

Values are means ± SEM (*n*).

BMI = body mass index; kg = kilograms.

None of the after-training values were significantly different from baseline ($P > 0.05$).

There was no significant differences in age, height, body mass, BMI, body fat %, or FFM at baseline or in response to training among the three *IGF1* promoter genotype groups ($P > 0.05$).

Table 3. Changes in 1- RM knee extensor strength, muscle volume, peak power with strength training (ST) in the trained and untrained leg in all subjects (*n* = 62-114)¶

	Trained leg	Untrained leg
1 RM (kg)	6.6 ± 0.3[bc]	2.2 ± 0.4[b]
Muscle Volume[1] (cm^3)	122 ± 6[bc]	-2 ± 4
Relative Peak Power at 50% of 1-RM (W)	20 ± 5[bc]	-7 ± 4
Relative Peak Power at 60% of 1-RM (W)	15 ± 6[ad]	-5 ± 4
Relative Peak Power at 70% of 1-RM (W)	13 ± 6[ad]	-7 ± 4
Relative Overall highest Peak Power (W)	22 ± 4[bc]	-3 ± 3
Absolute Peak Power (W)	31 ± 6[bc]	4 ± 3

Values are means ± SEM; W = watts; kg =kilograms

[1]Muscle volume of the knee extensors.

[a]Significantly greater than baseline ($P < 0.05$).

[b]Significantly greater than baseline ($P < 0.001$).

[c]Significantly different than the untrained leg ($P < 0.001$).

[d]Significantly different than the untrained leg ($P < 0.05$).

¶Sample size variability was due to missing data points for muscle phenotypes.

Table 4. *IGF1* CA genotype frequency for all subjects.

Genotype	Total Subjects (%)	Total Caucasians (%)	Total African-Americans (%)
192/192	36 (32)	31 (36)	5 (18)
192/-	55 (48)	42 (49)	13 (46)
Non-carriers of the 192 Allele	23 (20)	13 (15)	10 (36)

CA = cytosine adenine

192 allele is equivalent to 19 CA repeats

Table 5a. Baseline differences in peak power in the trained leg by *IGF1* genotype in all subjects.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Relative Peak Power at 50% of 1 RM (W)	330.5 ± 15.0* (26)	357.1 ± 12.7 (37)	388.7 ± 18.2 (18)
Relative Peak Power at 60% of 1 RM (W)	325.6 ± 16.0* (26)	351.3 ± 13.5 (37)	389.2 ± 19.4 (18)
Relative Peak Power at 70% of 1 RM (W)	295.8 ± 14.6* (32)	326.0 ± 12.3 (45)	351.5 ± 17.6 (22)
Relative Overall highest Peak Power (W)	317.6 ± 13.5* (32)	350.4 ± 11.4 (45)	380.2 ± 16.3 (22)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.

*Significantly less than the All other Genotypes group when covarying for age, sex and baseline FFM ($P < 0.05$).

Table 5b. Baseline differences in peak power in the trained leg by *IGF1* genotype in women.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Relative Peak Power at 50% of 1 RM (W)	224.3 ± 14.8* (12)	243.4 ± 11.5 (21)	284.2 ± 18.6 (8)
Relative Peak Power at 60% of 1 RM (W)	223.8 ± 15.8 (12)	235.2 ± 12.3 (21)	283.7 ± 19.9 (8)
Relative Peak Power at 70% of 1 RM (W)	211.0 ± 13.7* (17)	226.4 ± 11.2 (27)	270.1 ± 17.2 (11)
Relative Overall highest Peak Power (W)	224.1 ± 12.7* (17)	241.5 ± 10.4* (27)	293.4 ± 16.0 (11)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.

*Significantly less than the All other Genotypes group when covarying for age, sex and baseline FFM ($P < 0.05$).

Table 5c. Baseline differences in peak power in the trained leg by *IGF1* genotype in men.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Relative Peak Power at 50% of 1 RM (W)	428.4 ± 24.7 (14)	465.4 ± 22.3 (16)	505.7 ± 29.1 (10)
Relative Peak Power at 60% of 1 RM (W)	421.1 ± 26.0 (14)	460.4 ± 23.5 (16)	508.7 ± 30.6 (10)
Relative Peak Power at 70% of 1 RM (W)	396.6 ± 25.6 (15)	436.9 ± 22.7 (18)	470.6 ± 30.0 (11)
Relative Overall highest Peak Power (W)	428.1 ± 23.4 (15)	473.4 ± 20.7 (18)	505.6 ± 27.5 (11)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.
There were no significant differences in any of the baseline power values among the three *IGF1* promoter genotype groups, when covarying for age, sex and baseline FFM ($P > 0.05$).

Table 6. Change in peak power with ST by *IGF1* genotype in all subjects.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Absolute Peak Power (W)	12.9 ± 11.6 (20)	27.6 ± 9.6 (30)	18.9 ± 13.4 (15)
Relative Peak Power at 50% of 1 RM (W)	25.6 ± 9.8 (18)	22.8 ± 9.3 (24)	18.2 ± 13.8 (15)
Relative Peak Power at 60% of 1 RM (W)	12.8 ± 9.3 (17)	21.6 ± 10.0 (26)	3.8 ± 12.0 (15)
Relative Peak Power at 70% of 1 RM (W)	9.4 ± 9.8 (24)	22.6 ± 8.4 (33)	0.8 ± 12.4 (15)
Relative Overall highest Peak Power (W)	19.2 ± 9.1 (25)	28.4 ± 7.6 (36)	16.8 ± 10.7 (18)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.
Absolute and relative peak power change scores did not differ significantly among the *IGF1* promoter genotype groups when covarying for age, sex and baseline FFM ($P > 0.05$).

Table 7a. Baseline differences in peak power in the trained leg by *IGF1* genotype in Caucasians.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Relative Peak Power at 50% of 1 RM (W)	345.0 ± 16.3 (23)	364.3 ± 14.3 (30)	404.5 ± 25.3 (10)
Relative Peak Power at 60% of 1 RM (W)	342.3 ± 17.0 (23)	355.6 ± 14.9 (30)	400.3 ± 26.4 (10)
Relative Peak Power at 70% of 1 RM (W)	305.4 ± 15.1 (28)	326.9 ± 13.0 (37)	346.6 ± 23.6 (12)
Relative Overall highest Peak Power (W)	326.9 ± 14.3 (28)	352.7 ± 12.3 (37)	379.0 ± 22.3 (12)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.
There were no significant differences in any of the baseline power values among the three *IGF1* promoter genotype groups, when covarying for age, sex and baseline FFM (P > 0.05).

Table 7b. Change in peak power with ST by *IGF1* genotype in Caucasians.

	192 Homozygotes	192 Heterozygotes	All other Genotypes	
Absolute Peak Power (W)	6.0 ± 12.8 (17)	29.9 ± 10.6 (25)	39.2 ± 17.7 (9)	
Relative Peak Power at 50% of 1 RM (W)	17.2 ± 12.9 (15)	23.8 ± 10.9 (21)	26.8 ± 18.2 (8)	
Relative Peak Power at 60% of 1 RM (W)	4.7 ± 9.8 (14)	21.6 ± 11.3 (23)	12.3 ± 17.7 (8)	
Relative Peak Power at 70% of 1 RM (W)	6.2 ± 9.9 (21)	18.1 ± 8.7 (28)	11.6 ± 17.9 (7)	
Relative Overall highest Peak Power (W)	17.7 ± 9.8 (22)	24.9 ± 8.3 (31)	24.9 ± 15.8 (9)	

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.
Absolute and relative peak power change scores did not differ significantly among the *IGF1* promoter genotype groups when covarying for age, sex and baseline FFM ($P > 0.05$).

Table 7c. Baseline differences in peak power in the trained leg by *IGF1* genotype in African-American

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Relative Peak Power at 50% of 1 RM (W)	262.1 ± 44.1 (3)	314.1 ± 28.4 (7)	363.7 ± 25.3 (8)
Relative Peak Power at 60% of 1 RM (W)	236.2 ± 48.4 (3)	321.9 ± 31.2 (7)	369.9 ± 27.9 (8)
Relative Peak Power at 70% of 1 RM (W)	224.9 ± 44.8* (4)	307.2 ± 29.8 (8)	370.7 ± 25.7 (10)
Relative Overall highest Peak Power (W)	261.5 ± 40.7* (4)	322.9 ± 27.1 (8)	391.3 ± 23.3 (10)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.

*Significantly less than All Other Genotypes group when covarying for age, sex and baseline FFM ($P < 0.05$).

Table 7d. Change in peak power with ST by *IGF1* genotype in African-Americans.

	192 Homozygotes	192 Heterozygotes	All other Genotypes
Absolute Peak Power (W)	81.4 ± 21.9* (3)	0.8 ± 20.7 (5)	12.1 ± 14.7 (6)
Relative Peak Power at 50% of 1 RM (W)	61.9 ± 20.5 (3)	22.7 ± 25.2 (3)	7.8 ± 12.6 (7)
Relative Peak Power at 60% of 1 RM (W)	59.1 ± 17.9* (3)	9.9 ± 22.0 (3)	20.8 ± 11.0 (7)
Relative Peak Power at 70% of 1 RM (W)	38.4 ± 40.1 (3)	53.3 ± 27.5 (5)	15.0 ± 22.8 (8)
Relative Overall highest Peak Power (W)	27.2 ± 28.4 (3)	59.0 ± 20.1 (5)	4.7 ± 15.3 (9)

Values are least-square means ± SEM (*n*) when covarying for age, sex and baseline FFM ; W = watts.

* Significantly more than All Other Genotypes group when covarying for age, sex and baseline FFM ($P < 0.05$).

APPENDIX A:
RESEARCH HYPOTHESES, SIGNIFICANCE, DELIMITATIONS, LIMITATIONS, OPERATIONAL DEFINITIONS

Research Hypotheses

1. *IGF1* genotype will be significantly associated with variation in baseline knee extensor peak power in older adults.
2. *IGF1* genotype will be significantly associated with changes in absolute and relative knee extensor peak power after 10 weeks of ST in older adults.

Significance

The results of this study when combined with those from other studies will help generate new hypotheses for a better understanding of the role of genetics in muscle power development. The ultimate goal of this area of research will be to provide better screening procedures and individualized exercise prescription for the prevention and treatment of sarcopenia, but achieving this goal will require many more future studies.

Delimitations

1. The subject pool will be delimited to approximately 114 older men and women between the ages of 50 and 85 years who volunteer as study participants and whose *IGF1* genotype data is available.
2. Participation in the study will be limited to healthy participants free of musculoskeletal or cardiovascular disease who live within 20 minutes of our training facility and who respond to our mailed advertisements of the study.

3. Based on previous research, subjects will be divided into three genotype groups for determining the effect of the *IGF1* promoter polymorphism: 192 homozygotes, 192 heterozygotes, or non-carriers of the 192 allele.

Limitations

1. Due to the longitudinal design of the investigation and multiple variables within each genotype group, most of the dependent variables have some missing data points. Therefore, sample size will vary among the various dependent variables from 57 to 99.
2. Study participants will be volunteers and not randomly selected from the general population. As such there may be selection biases that diminish the ability to generalize the results of the study to individuals who do not conform to the sample population's characteristics, such as age, race, gender, body size, physical activity, motivation levels, etc.
3. Subjects will self-report many factors related to health and lifestyle such as physical activity habits, dietary habits, medication regimens, and medical conditions. Because the accuracy of these reports cannot be verified, it is possible that inaccurate self-reports may occur, which could adversely affect the results of this study.
4. It will not be possible to verify compliance of factors that are not being self reported, but are part of what subjects are asked to do outside of training during the study period (e.g. maintain diet and activity patterns and not change their medications).

5. Genotypes other than the *IGF1* cytosine adenine (CA) dinucleotide repeat polymorphism will not be assessed in the proposed study. It is possible that the *IGF1* polymorphism effects are present only in the presence of a specific, but unknown, genetic background (epistasis).
6. Polymorphisms in the regions flanking the *IGF1* gene will not be identified or assessed in the genomic material for this study. It is therefore possible that any reported genotype effect is due to linkage disequilibrium between the *IGF1* cytosine adenine (CA) dinucleotide repeat polymorphism and a distinct and putative polymorphism at another locus within the same chromosome.

Operational Definitions

1. **1-RM:** Refers to the maximal resistance that could be moved a single time through the full range of motion (ROM) with proper form.
2. **5-RM:** Refers to the maximum amount of resistance an individual can move through a complete range of motion only five times.
3. **CA dinucleotide repeat polymorphism (*IGF1* gene):** This polymorphism is identified by the length of a CA dinuceotide repeat found in the promoter region of the *IGF1* gene. It can be 16 to 22 dinucleotides in length (99% of population) and is located at nucleotide position 1087 – 1127 in the human *IGF1* DNA sequence in the original human *IGF1* DNA sequence Genbank accession number AY260957. RS# 10665874. For the *IGF1* promoter polymorphism, subjects would be classified into 3 genotype groups as previously reported in the literature: 192 homozygotes, 192 heterozygotes or non-carriers of the 192 allele.

4. **Computed tomography (CT):** A technique for assessing regional muscle size based on the examination of axial scans of the thigh. Visual images are created from the measurement of the intensity of x-rays and analyzed to measure cross-sectional area. The images are based on the attenuation of x-rays as they pass through the body. Attenuation scores are measured in Hounsfield units, which depend upon the level of absorption of emitted x-ray beams, -1000 air to +1000 bone. Skeletal muscle is typically 0 to 100 and adipose tissue is usually -190 to -30.
5. **Functional abilities:** An individual's capacity to perform activities of daily living such as walking up and down a flight of stairs or carrying groceries.
6. ***IGF1* gene:** *IGF1* is located on chromosome 12 (12q22-q24.1), and contains 6 exons, four of which are subject to alternative splicing.
7. **IGF-I protein:** Human IGF-I is a 70-residue polypeptide with growth-promoting and metabolic actions. It is present in both non-muscle and muscle tissues. Skeletal muscle is known to be affected by the autocrine/paracrine action of IGF-I.
8. **Lengthening phase:** Formally called the eccentric phase. The phase of muscle action in which the muscle lengthens as it resists the external forces of the knee extension machine, as exemplified in this study by slowly lowering the lower leg (knee flexion) after a full range of motion has been reached for the knee extension exercise.
9. **Muscle Power:** Calculated as the product of torque and angular velocity and reported in watts. Torque is calculated by multiplying the force exerted by the

distance from the knee joint to the force sensor (0.34925 m) and reported in N-m. Angular velocity is reported as rad $\cdot$ s^{-1}.

10. **Muscle volume:** Total quadriceps muscle volume will be determined by Medical Image Processing, Analysis, and Visualisation (MIPAV) software through the utilization of 8-11 axial thigh slices obtained from the CT scan.
11. **Range of motion (ROM):** The full ROM would be set at 165 degrees of knee extension.
12. **Rating of perceived exertion (RPE):** A subjective determination of how much effort the subject feels they are exerting. A 6-20 scale would be used with 6 being very, very light work, and 20 the hardest possible work.
13. **Sarcopenia:** A condition characterized by the loss of muscle size, quality, and function that occurs with aging. This typically leads to or exacerbates ailments such as osteoporosis and loss of functional independence.
14. **Sedentary:** A description for individuals who are not physically active. In the proposed study this term describes individuals who, on average, have exercised aerobically for less than 20 minutes per day less than 2 times per week and have not performed any type of regular resistance training over the past six months.
15. **Shortening phase:** Formally called the concentric phase. The phase of muscle action in which the muscle shortens as it resists the external forces of the knee extension machine, as exemplified in this study by movement of raising the lower leg (knee extension) until the subject reaches full range of motion on the knee extension exercise.

16. **Unilateral knee extension (KE) exercise:** In the seated position, subjects would extend their lower leg against a resistance. Only one leg would be used while the other leg stays motionless.

APPENDIX B:

LITERATURE REVIEW

The following review of literature provides background information related to the topic of *IGF1* gene polymorphisms, muscle power and ST adaptations in older adults. This review will focus on the following topics: 1) Causes and consequences of sarcopenia, 2) Potential mechanisms of sarcopenia, 3) Muscle power decline with age, 4) ST as an intervention against the negative consequences of sarcopenia, 5) Variability in muscle size and function in response to aging and ST, 6) Genetic variability in muscle phenotypes related to sarcopenia, 7) Physiology of *IGF1* promoter polymorphism and the recommendations for future studies.

Causes and consequences of sarcopenia.

The term sarcopenia comes from the Greek words *sarx* (flesh) and *penia* (loss), literally meaning loss of flesh. It refers to the loss of skeletal muscle mass with aging which subsequently affects performance and muscle function, including loss of strength, muscle quality, and power (156,167,220). No single factor has been identified to explain the aging-related loss of muscle size or function, because sarcopenia is a multifactorial condition that occurs naturally with aging, though its starting point and consequences vary substantially. However, there is significant inter-individual variability in the magnitude of loss in muscle mass and muscle function with age, as well as the factors that explain these losses. Some of the major factors that appear to contribute to sarcopenia are decreases in alpha motor neurons, motor units, protein synthesis, expression of myosin heavy chain (MHC), and a rise in catabolic stimuli, such as cytokines (e.g. IL-6 and TNF-α) (62,36,170,245).

Hormonal and growth factors include, reductions in the level of sex steroids and impairments in the growth hormone (GH)/insulin-like growth factor (IGF) pathway (259,277,18,62). There are also environmental factors, such as nutrition and physical inactivity that can have a profound influence on sarcopenia (185,62,205).

The first study to define and determine the prevalence of sarcopenia in a large group of individuals was the New Mexico study reported by Baumgartner et al (19). In this study, sarcopenia was defined as having two SD below the mean appendicular muscle mass for healthy young adults. The authors reported that in elderly Hispanic and Caucasian males and females the prevalence of sarcopenia increased from 13 to 24% of persons aged 65-70 years, to over 50% of those older than 80 years. In addition, sarcopenic women had 3.6 times higher rates of disability, and sarcopenic men had 4.1 times higher disability rates compared with study participants with normal muscle mass. In another study in which DXA was used to measure muscle mass, Iannuzzi-Sucich et al (124) reported that the prevalence of sarcopenia was 22.6% for women aged 64-93 years and 26.8% for men aged 64-92 years. These authors also reported that the prevalence of sarcopenia for women and men older than 80 years was 31% and 45%, respectively. Similarly, Janssen et al (130) used whole body MRI to examine skeletal muscle mass and distribution in a large cohort of 468 men and women from 18 to 88 yr of age. They observed a decline in whole body skeletal muscle beginning in the third decade; however this loss did not become substantial until the end of the fifth decade. An important finding of this study was that the loss of muscle mass with aging was greater in the lower body in men and women. This finding may reflect decreased activity or altered patterns of activity of

the lower extremity muscles with aging and has important implications for functional mobility and disability.

In addition to these studies, the losses of muscle mass and muscle function due to sarcopenia have been well-documented in several recent cross-sectional and longitudinal studies (90,57,134,79,161,165), and have many significant health consequences ranging from decreases in functional ability to increased mortality risk. These consequences include: increased risk of falls (162,255), hip fractures (5), glucose intolerance (25) bone mineral density loss (257,252), and physical disability (295). Most of the studies investigating the functional implications of sarcopenia have assessed the relation between lower limb strength or power (or both) and function in tasks such as stair climbing, rising from a chair, or walking (48,217,26,204,21). Finally, it has been shown that sarcopenia is associated with increased mortality(180,181,182). Miller et al (182) showed that corrected arm muscle area is a better predictor of long term mortality than BMI, which is often used as a predictor of mortality in older adults. Also, several studies have reported an association between low muscle strength and increased mortality rates (155,223). For example, Metter et al (180) reported that both grip strength and change in grip strength were predictors of mortality, independent of physical activity or muscle mass.

Using the standard criteria for sarcopenia, Baumgartner et al (19) estimated the prevalence of sarcopenia to be about 9 million in the U.S. With an aging society, this is estimated to expand significantly and become a major medical cost. Demographic data indicate that the populations of most western nations are growing older. In the

United States for example, census data has estimated that the number of people considered to be aged (>60 years old) will more than double between the years of 1990 and 2030. Consequently, health care costs will increase for the elderly. Thus with an aging society, it is imperative from a public health perspective to address this natural aging process, through a better understanding of its causes, prevalence and treatment.

Potential mechanisms of sarcopenia.

No single cause has been identified to explain the decline of muscle size or function with age. Yet, many interrelated factors likely contribute. A loss of alpha motor neurons, declines in testosterone and estrogen, growth hormone, IGF-I, protein synthesis, changes in myosin heavy chain (MHC) gene expression, and an elevation in catabolic stimuli, including cytokines, are examples of some of the major factors leading to sarcopenia.(153).

The total number of central nervous system and muscle neurons is known to decrease with age (234,32), resulting in a preferential loss of the fast motor unit (61,63). This results in a reinervation by slow motor units, which transforms them into the slow myosin type (63), resulting in an increase in motor unit size and a decrease in the number of fibers that produce high force and velocity. It can also result in reduced force and/or power production of the entire muscle due to the loss of the most powerful muscle fibers. Nevertheless, Urbanchek et al. (287) reported that only 11% of the decrease in muscle force production was attributable to denervated fibers. Furthermore, some recent evidence suggests that the loss of motor neurons with aging is not as considerable as previous reports suggested (186).

In addition to the loss of fast motor units, muscle contractile and mitochondrial protein synthesis rates decline with aging (8,193,235,154), as do whole body muscle protein synthesis rates and MHC levels (8,300,109). Also, several hormones such as testosterone, estrogen, growth hormone, and IGF-I have an anabolic effect on muscle, and decrease with age (13,285,106,213,293). Moreover, catabolic stimuli, including cytokines, increase with aging (241,264).

Muscle power decline with age.

Muscle power (i.e., the rate of force production) accounts for a greater amount of the variance in physical performance than strength in older adults (21,79) and deteriorates at a faster rate than strength with advancing age (16,179,260). Although the literature is not as extensive for investigating muscle power losses as strength losses with aging, recent studies have focused on the changes in power with aging and with exercise training. Most recent aging studies, showing a greater decline in maximal power than decline in isometric and dynamic strength have used derivatives of the Hill's (1938) equation to calculate power from the f-v relationship (194,271,278), but have not directly measured movement velocity, an important component of power.

This lack of data on muscle power and the elderly is partially attributable to the difficulty in safely and accurately measuring power (66). The use of isokinetic dynamometers allow for power to be estimated in a single muscle group based on peak torque, but this measurement does not consider the power needed to accomplish daily tasks at various external resistances and overcome speed (167). Because velocity is pre-determined by the tester and the device, instead of the subject being

tested, the velocity component of power is not directly assessed with isokinetic, which explains why data is lacking for power losses with aging. **I**n addition, elevated antagonist muscle activity in the elderly may limit the full movement efficiency depending on the type of muscle contraction and the movement velocity. Earlier measurement of power employed vertical jumping from a force platform (72,92), which functioned similar to a scale, whereby muscle power is the product of force (after subtraction of body weight from the vertical component of the ground reaction force) and the movement velocity. This type of measurement may not be safe for older adults. Moreover, the subject must move his/her body mass, which likely represents a higher than optimal external load for peak power production based on the force-velocity curve (167). The nature of the force/ velocity relationship dictates that power will have its own distinct relationships with force and velocity of movement. Thus, there is an optimum force and an optimum velocity at which maximum power is developed. In isolated animal muscle, these correspond to about 30% of P_o and 25-30% of V_{max}, respectively (167). However, measurements of force and velocity and power/velocity relationships in humans *in vivo* represent the resultant of relatively complex situations, as human muscles are attached to bones via tendons that cross over one or two articular joints in order to produce movement. Not only must the contractile elements of muscle cells be considered, but also factors such as neural influences, muscle architecture and intracellular connective tissue. The optimal values of force and speed for maximum power production *in vivo* may therefore be different from those recorded in isolated muscles or skinned single fiber preparations.

The aforementioned difficulty in safely and accurately measuring power (167) was addressed in several investigations (66,76,127,134) reporting peak power as the highest average power obtained during multiple trials of a power test, as opposed to the highest power value attained during a single trial. The highest peak power (i.e., the highest combination of force and velocity that occurs simultaneously during a single trial) might be a more accurate measure of the explosive capacity of the trained musculature than average (area under curve) power of a single trial. This is because average power includes two phases of movement that represent reduced power. The first is at the beginning of the movement when one is trying to overcome inertial forces and the other is near the end of the movement when co-contraction of the antagonist muscle group produces a reduced force and velocity. Although some previous investigations did exclude data from the first and last 5% of the range of movement in the power tests (21,76,79), these studies still used the average power for a given trial, and reported it as peak power.

To address the safety concerns associated with power testing using a force platform, Bassey and Short (17) invented an apparatus that measured average leg extensor power from force against a pedal that accelerates a flywheel of known inertia. However, older subjects were still required to use a higher percentage of their maximal power capacity because of the fixed inertia characteristic of the apparatus (167), but this problem has been since corrected by the development of a variable inertia testing apparatus (208). More recently, Delmonico et al (58) reported the measurement of peak power during a single trial, rather than average power throughout the range of movement in a trial. A single maximal knee extension

repetition was performed in older adults by using a machine equipped with load cell force transducers and position sensors to detect rotary motion at the joint. Peak power is calculated by filtering power data points during a single knee extension trial with a 10^{th} order Butterworth filter. The use of this dynamic pneumatic resistance equipment for the evaluation for muscle power has since then been used for the evaluation of muscle power in most recent studies (53,114) and has been shown to be a reliable, valid and safe method of muscle power testing in older adults (34).

Izquierdo et al (128) determined the optimal loads for maximal power production and found that peak power is maximized at 30 – 45% of peak strength for the upper extremity and at 60-70% for the lower extremity in middle aged and older adults. Moreover, their results confirm previous data showing peak power decreases with increasing age to a greater extent than strength. This work is supported by more recent data reported by Macaluso and De Vito (166) who found that maximal peak (average) power is obtained at ~ 60% of maximum isometric strength in both young and older women, and this peak power is 61% lower in the older women. They also reported that power is influenced to a greater extent with aging than isometric strength. In contrast to these findings, Cuoco et al.(48) reported that lower external loads (~ 40% of leg press 1- RM) explained more of the variability in normal gait speed in the elderly than did power at higher external loads (~ 70% of 1- RM). Habitual gait speed is known to be a predictor of future disability, thus the authors suggest that lower external resistances should be used when evaluating peak power in older adults (48). More recently, the study by Puthoff and Nielsen (217) reported that subjects reached peak power at an average relative intensity of 62% of 1- RM unlike

previous studies that have reported peak power occurring at 70% of 1- RM or higher (21,76,20). These authors reported that differences in testing protocols used in these studies may account for the power value differences; however they recommend that future investigators should be cautioned in using power at a predetermined relative intensity to represent peak power values for all subjects.

Previous cross sectional data suggest that the decline in peak muscle power with age is associated with muscle structure and function, tendon characteristics, and sarcopenia in specific muscle groups (242). In that investigation, 169 women and 89 men between 18 and 88 years were studied, and muscle force and power were assessed by jumping mechanography. These healthy subjects showed a difference of > 50% between the ages of 20 and 80 without a reduction in muscle cross sectional area suggesting that power declines might central role in the aging process. Additionally, because there is a general consensus that the relationship between muscle power and function is stronger than that of strength and functional abilities in the elderly (21,48,217,269), determining the age-related causes of decreased muscle power provides important and relevant information to the understanding of sarcopenia. Bassey et al (16) examined leg extensor power in elderly (~ 88 yrs old) patients in a chronic care facility using a custom built rig that measured maximal power output over < 1 s of a single extension of one leg. They found that leg extensor power was significantly correlated with all functional ability measures which included time taken to rise from a chair, climb a flight of stairs and walk 6.1m. These data agree with findings obtained by Rantanen and Avela (221) that average leg extension power is a key factor that helps explain the increased prevalence of

mobility impairments in the elderly. Numerous recent studies have also added to the growing body of evidence that power has greater influence over functional capacity than strength (21,269,217). The functional capacity was assessed in these studies using various functional performance tests such as chair-rise time, stair-climb time, tandem gait, habitual gait, maximum gait and the short physical performance battery (SPPB).

Cross-sectional and longitudinal data from the BLSA (179) show age-associated reductions in power and isometric strength in the upper extremities in men and women over an average ~ 10 year period. Peak arm power was measured in 10 - 15 sec periods of maximal arm cranking using a bicycle which was converted and functioned as a drive shaft to power a generator. Strength and power declined beginning by age 40 in both women and men, but power declines were ~ 10% greater than strength losses in men, while no significant declines were found in women. The differences between the changes in power and strength with age in men support the hypothesis that there are variables other than strength, such as movement velocity, that influence power reductions. This finding confirmed an earlier study by Skelton et al (260) who found that between the ages of 65 and 89 years, power declines at a rate of ~ 3 – 4% per year, which is higher than the rate of isometric strength loss (~ 1 – 2% per year). Runge et al (242) also reported that there is a significant decrease in muscle power between the ages of 20 and 80 years, without a decline in muscle CSA. Most recently, Petrella et al (211) examined age and gender differences in knee extensor strength and power in young (~ 26 yr old) and older (~ 63 yr old) men and women. The results showed that there were significant strength differences between

the young and older subjects, and there was also a significant difference between age groups in knee extension power when normalized for thigh muscle mass. In addition, older adults had a significant decrease in peak velocity over 10 repetitions of knee extension exercise, indicating that attenuation of velocity in older adults may likely be a contributing factor for decreases in power. This decrease in velocity may also contribute to increased risk of falls and mobility loss in the elderly.

Aging-related declines in muscle strength and power are related to changes in the number of motor units, lower muscle fascicle length and pennation angle, increases in connective tissue and fat infiltration, fiber type grouping, loss of type II fibers, and decreased expression of myosin heavy chain (MHC) proteins (8,141,151,159,187,195,271). The mechanisms that cause a more rapid decrease in power than strength with aging are not yet fully understood. However, because power is the product of force and velocity, variables that influence either of these two factors will affect peak power (167). Thus, many of the mechanisms that influence muscle strength decline with aging are likely to be at least partially responsible for the related decreases in power with advancing age. Additionally, specific changes that might influence muscle contraction speed will have a more significant impact on peak power than strength. For example, with aging there is a preferential loss of type II skeletal muscle fiber number and size. However, according to a recent study by D'Antona et al. (50), this selective atrophy of type II muscle fibers, is caused by the decrease in physical activity that occurs with aging, rather than aging per se. Furthermore, older skeletal muscle has been shown to be more likely to express more than one MHC isoform than the skeletal muscle of young subjects (145). Animal

studies report that type II skeletal muscle fibers are capable of a four-fold greater power and force output and a faster shortening speed than type I fibers (167). The loss of type II fiber size leads to the decreased expression of fast MHC isoforms, which would likely have a significant impact on power output (108), and supports the evidence of change from fast to slow motor units with aging (291).

Other potential mechanisms have also been identified, which include increased tendon stiffness with aging (167) and neural influences, which include dopaminergic neuron loss in the substantia nigra. This could result in a decrease in coordination, movement speed, and power. Furthermore, decreases in the sliding speed of actin on myosin with aging may play an important role in the observed power decline with advancing age. For example, Hook et al (117) reported an 18 – 25% age-associated reduction in the speed of actin filaments on myosin from 62 single fibers. The mechanisms underlying the aging-related slowing of motility speed remain unknown, but it is hypothesized that posttranslational modifications of myosin by oxidative stress, glycosylation, or variations in muscle protein expression might explain this decline in the intrinsic speed of the myosin molecule with age. In addition, a recent study by Thom et al (271) reported that fascicle shortening and the associated loss of sarcomeres in series is thought to account for a significant portion of the decline in muscle power observed in old age.

ST as an intervention against the negative consequences of sarcopenia.

As a result of the increased prevalence of sarcopenia, the resulting health care costs and detrimental physical consequences, it is imperative from a public health perspective to design safe and effective interventions for the prevention or delay of

sarcopenia, without the adverse side effects of many pharmacological interventions. Recent reports indicate that the administration of growth hormone, one of the more commonly recommended interventions for sarcopenia, should not be used for this purpose due to its untoward side effects and questionable efficacy (24,190). Therefore, until future research suggests otherwise, ST should be the intervention of choice for sarcopenia due to the substantial evidence for its efficacy within a very short time frame and safety (121,214,122,238,74). Several training studies have shown the efficacy of ST in increasing muscle strength and muscle mass in men and women aged 50-98 yrs (258,74,126,147,82). Some ST studies in older adults have also examined the muscle function changes that occur at the muscle fiber level. Data show that type I and type II muscle fibers in older adults maintain the ability to undergo hypertrophy with ST (44,82,97), but some investigations found that there was only slight or no change in fiber areas (94,120). Changes in fiber size with ST are ~ 10%, which is typically greater than at the level of a whole muscle group. This may be at least partly because MRI and CT assessment of whole muscles or muscle groups also measures other tissues (e.g. connective tissue), which are not apt to experience the same magnitude of change as muscle tissue. In addition several studies have found evidence for MHC II subtype transformations with ST in older adults, with MHC IIb changing to IIab to IIa, which is a similar response that occurs in younger adults (98,108,254). However, one investigation reported an increase in MHC I expression with ST (302), which could be attributed to a lower intensity training protocol in that investigation. It has been suggested that this lower intensity training program was not enough of a stimulus to recruit the fast MUs necessary for

optimal increases in MHC II expression. At the muscle fiber level, Trappe et al (282,284)) found that in older men and women, skeletal muscle fibers increase in size, strength, and power with 12 weeks of ST. Other investigations report increases in protein synthesis in older adults with ST along with improvement in strength (109,300). Muscle quality (i.e. strength per unit of muscle mass) has been shown to improve with ST in older adults (126,280,300). Moreover, as muscle architecture plays an important biomechanical role in the ability of the muscle to produce force, the effect of resistance exercise on muscle architecture in older adults has been examined in numerous recent studies (188,225,226,265). The recurrent finding is that there is an increase in muscle fascicle pennation angle following resistance exercise, which means that more sarcomeres are added in parallel, allowing muscles to produce more force across all concentric contraction speeds. There is contradictory evidence, however with regards to whether muscle fascicle length of older adults changes following resistance exercise, with one study showing no change (188) and others finding an increase in fascicle length (226,225). Finally, the muscle adaptations due to ST have been shown to positively affect functional ability in elderly men and women (244,69).Because muscle power accounts for a greater percentage of the variance in functional abilities than strength (21,79) and deteriorates at a faster rate than strength with advancing age (16,179,260), recent studies have more often focused on the effect of ST on muscle power (20,58,66,73,76,97,134,112,53,227,28).

A randomized study by Earles et al (66) compared the effects of a high-velocity ST program combined with moderate non-resistive exercise to an intervention of walking on leg press and knee extension peak power in men and women over the age

of 70.Power improved significantly in the high-velocity ST group only for leg press (22%) and knee extension (increases of 50%, 77%, and 141% when power was tested at external resistances of 50%, 60%, and 70% of body weight, respectively). However, these improvements in power did not lead to improvements in functional abilities, although their cohort was considered high functioning at baseline. A more recent randomized study by Fielding et al. (76) examined 30 older women with mild functional limitations and compared the changes in skeletal muscle power between 16 weeks of high-velocity ST and a more traditional, low-velocity ST intervention. The results indicate that although leg press and knee extensor 1-RM strength increased similarly in both groups with ST, leg press peak power increased significantly more in a high-velocity group (97%) than in a low-velocity group (45%). The conclusion was that higher-velocity training programs might be more efficacious for increasing peak power in older individuals with functional impairments. These data agree with recent findings that a 10-week power training (PT) program (three 8-10 repetition sets performed as fast a possible at 60% of 1-RM) produced greater improvement in muscular power and functional performance than the traditional resistance training (TRT) (three 8-10 repetition sets with 2-3 s contractions at 60% of 1-RM) in older men (28).

In contrast to the above findings a recent study by Henwood et al. (112) observed similar improvements in maximal strength, peak and average muscle power, and functional performance after traditional resistance and high velocity varied resistance training. These results were similar to the findings of a randomized control trial done by Reid et al (227), in which a short-term intervention of high-velocity power training

and traditional slower velocity progressive training yielded similar increases of lower extremity power in the mobility-impaired elderly.

Moreover, it is still not well established whether a high velocity training program is well tolerated by older subjects (68) especially subjects who are frail and could benefit the most from increased muscle power. Furthermore, most power training studies done in older adults have reported several adverse events. One study, for example, reported a case of disc herniation that may have resulted from the training program (66). Other injuries include back pain (66), exacerbation of pre-existing osteoarthritis (76,113,53), minor strains (53), tendonitis (53), plantar fasciitis (76) and unspecified injuries leading to drop-out (184). A recent power-training study done with the largest group of subjects (n =112), reported that since all the training injuries occurred during high-load (80% of 1-RM) training, lower-load training (50% 1-RM) might be undertaken to reduce the risk of injury, even though the benefits to strength and endurance might be lower.

Several studies that examined peak power used lower-velocity ST protocols that have extensive track records for being generally safe for older subjects (75,134,261). In these investigations, muscle power increased significantly with ST, ranging from ~ 18 – 28%, lower than some studies using higher velocities (184,28), though the increases in strength were greater due to specificity of training.

In an earlier investigation, Fiatarone et al.(75) conducted a randomized, placebo-controlled trial comparing ST, multinutrient supplementation, both interventions, and neither in 100 frail nursing home residents over a 10-week period. Power, as measured by stair-climbing performance improved in the exercise group

compared with the non-exerciser group (28.4% vs. 3.6%). These data indicated that there is a relationship between power adaptations to ST and functional ability. That study was followed by a report by Skelton et al (261), who found that in 20 relatively healthy, independent elderly (76 to 93 years) women, knee extension power increased by 18% (as measured by the Nottingham Power Rig developed by Bassey and Short (17) when adjusted for body weight. More recent data reported by De Vito et al.(54) examined the effects of a 12 week of a low-intensity general conditioning program on maximal power in 20 elderly women (~ 63 yrs) randomized to a training or control group. Peak power was determined at baseline and after the training regimen via vertical jump on a force platform. Peak power increased significantly in the training group, but did not change in the control group. The authors suggested that this increase in power could be due to improvements in neuromuscular activation. Additionally, Jozsi et al.(134) reported that with ST in men and women age 56-66 years, there was an increase in knee extensor and arm flexor power with ST of 30% and 18%, respectively. These increases in peak power were independent of age or sex and occurred at 40% and 60% of 1 RM, and were similar to the changes observed in younger subjects. Izquierdo et al. (127) also reported that 16 weeks of ST resulted in large gains in strength and power load characteristics of the upper and lower extremity musculature, but the pattern of strength and power development seemed to differ between the upper and lower extremities in middle aged and older men. These studies, when taken together, suggest that both traditional and higher-velocity ST interventions are capable of increasing muscle power in older adults.

Earlier reports (66,76,127,134) on the effects of strength training (ST) on muscle power also did not report how the training affected power per unit of the muscle involvement (muscle power quality, MPQ), or peak movement velocity (PV), the latter possibly being an important component of power and possibly functional abilities in the elderly. The expression of peak power and PV normalized for muscle volume allows better understanding of potential mechanisms (e.g., hypertrophy and neuromuscular adaptations) for training-induced adaptations. It is also important when comparing groups who possess different amounts of muscle mass, such as men compared to women. Most recently, Delmonico et al.(58) reported the effects of a 10-wk, moderate velocity ST intervention on peak knee extensor power in relatively healthy older men (n = 30) and women (n = 32). Results showed that peak power (PP) increased significantly in both men and women at the same absolute (same absolute resistance before and after ST) and relative (70% of 1 RM at baseline and 70% of the improved 1 RM after ST) external loads. In addition, men and women both increased their absolute peak movement velocity with ST, and there was a significant 9% training-induced increase in MPQ in women, but no change in men. This latter finding indicates that women may not rely on muscle hypertrophy as much as men to improve muscle function with training. This could possibly be due to some type of neuromuscular adaptation that compensates for the reduced capacity of women to undergo muscle hypertrophy with ST compared to men, resulting in a compensatory increase in power per unit of muscle. Support of a sex difference in MPQ comes from work by Trappe et al.(283,282)) who found that the response of skeletal muscle fibers to ST on peak power normalized for cell size and unloaded

shortening velocity differ with the same training stimulus between men and women. However, no change in muscle fiber unloaded shortening velocity or normalized peak power was found in older women, indicating a sex difference in response to ST, although the cause for this difference is unclear.

Muscle power is a more complex phenotype than strength, thus there may be more interrelated factors that influence peak power changes with ST than are responsible for muscle strength changes alone. First, there are possible preferential increases in type II fibers leading to overall increases in muscle mass, which in turn leads to enhanced force production and muscle fiber shortening (76). Previous data has shown that adaptations to single MUs can help increase contraction speed with ST (290). Changes in MU function consist of earlier activation, shorter interspike intervals, and increased maximal firing rate (290). In addition, neural adaptations, including increased activation of the agonist muscle groups, decreased co-activation of the antagonist muscle groups, improved coordination and activation of synergistic muscles, and increased neural drive from the CNS, might lead to improvement in power with ST (167,84). Nevertheless, it may be problematic to directly examine these potential neurological components during power testing using electrophysiological methods because there are a host of physiological, mechanical, and electrical changes that happen during the contraction that might impact the correlation between signal amplitude and muscular force (167). Finally, tendon stiffness may be affected by ST, which may affect power changes. Maganaris et al (168) used an *in vivo* method for assessing tendon stiffness in older adults, and found that patellar tendons stiffened structurally and materially by ~ 65% in response to a

14-week ST intervention. The rate of muscle torque production also increased by ~ 27%, indicating that there is a faster contractile force transmission to the skeleton. Also since age differences in power persist even after accounting for muscle size, primarily from deficits in movement velocity (55,211) some studies have also examined changes in movement velocity using progressive resistance exercise as a stimulus and reported significant improvements (58,66,166). A recent study by Petrella et al (210) reported that the gains in concentric peak power during 16 weeks of progressive resistance exercise were differentially driven by gains in force and/or velocity among age groups. Of the components of peak power (force and velocity), marked improvements were found in both force and velocity among older adults while young adults only improved force (strength).

These data provide support for several mechanisms that might play a role in the changes in power with ST. However, there appears to be a great deal of inter-individual variability in the rate of decline in muscle mass and muscle function with aging, that contributes to the age related differences in power (172). A recent study by Kostka et al (148) reported that age contributed to the variability in quadriceps maximal short-term power, independent to quadriceps mass and optimal shortening velocity, probably reflective of age-related impairment of neural control to the muscular function and an increase in the proportion of connective tissue within the muscle (3).

Variability in muscle size and function in response to aging and ST.

Studies have demonstrated great inter-individual variability in the loss of muscle mass and strength with age (161,165). This variability remains, even after controlling

for physical activity levels (165). Moreover, muscle mass, strength, and power responses to ST vary substantially among individuals. In a previous investigation from our lab, after only nine weeks of a highly standardized quadriceps strength training program in a healthy and homogeneous group of 65 to 75 year old men and women, knee extension strength gains with ST ranged from 5 to 86 pounds (125). Muscle power changes with ST also are quite variable, with peak power ranging from – 19 to 126 W at the same absolute resistance, and peak movement velocity changes ranging from -1.1 to 2.7 rad/sec at the same absolute resistance (58). These data indicate that there are large inter-individual variations in muscle changes even in response to very short term, highly standardized strength training interventions. Studies here have also reported increases in quadriceps muscle volume with ST that range from 19 to 344 cm, further demonstrating the wide variation of inter-individual changes in muscle mass from ST (125). This large inter-individual variability and the fact that twin studies show that a major portion of the variance in strength and muscle mass can be accounted for by heredity, suggest that heredity and specific gene polymorphisms may explain a large portion of inter-individual differences in responses to ST.

Genetic variability in muscle phenotypes related to sarcopenia.

Results from heritability studies, genome wide scans, and candidate gene studies have suggested the presence of a genetic influence on baseline and ST-induced muscle phenotypes. The estimation of heritability of a specific trait is commonly estimated by the study in twins and families. The most common analysis of heritability is phenotype measurement between and among sets of monozygotic and

dizygotic twins. If a trait is completely determined by genetics, there would be correlation of 1.00 between sets of monozygotic twins, but a correlation of only ~ 0.50 between dizygotic twins, because dizygotic twins only share ~ 50% of their genetic makeup. However, skeletal muscle phenotypes are also influenced by many other factors beyond genetics, which can have an effect on the heritability estimate. Factors such as shared/non-shared environmental factors, additive/dominant genetic effects, and measurement error can influence these heritability estimates.

Several heritability studies have shown the influence of genetics on fat-free mass (FFM) at baseline. Bouchard et al (29), for example, estimated the transmissible variance of familial resemblance for FFM to be 40-50% in subjects from the Quebec Family Study. Other studies performed on monozygotic (MZ) and dizygotic (DZ) twin pairs have shown that the heritability in lean body mass ranges from 52-80% (6,198,251). A more recent twin data study in adults confirmed these heritability values from previous studies by reporting a heritability estimate of 77% for FFM in both men and women (105). Age and sex did not appear to be significant covariates of within pair differences. In contrast, a more recent heritability study on skeletal muscle traits in subjects of African descent reported that heritability may differ as a function of sex and age (215). In this study, the age-specific analysis showed that the heritability of leg lean mass was lower in older vs. younger individuals ($h(2) = 0.05$ vs. 0.23, respectively, $P = 0.1$). Also, sex was a significant covariate in the models ($P < 0.001$), although sex-specific differences in heritability varied depending on the lean mass phenotype analyzed. Another heritability study by Huygens et al. (123) reported a higher genetic influence on muscle mass by reporting that up to >90% of

the variance in baseline muscle mass is heritable in young male twins. With regard to skeletal muscle fiber composition, earlier heritability estimates suggest that muscle fiber type composition is over 90% genetically determined (146), but later studies indicate it is only around 45% (256). In addition, skeletal muscle enzyme activity also seems to be somewhat heritable, with estimates of 25 – 50% when adjusted for age and sex (30).

Twin studies indicate that strength has a moderate to high heritability, with different studies reporting a range of 30 – 80% depending on the population studied. Frederiksen et al (81) reported that in 1,757 Danish twin pairs aged 45 - 96 years, handgrip strength heritability is 52% but can be as high as 62% when examining only healthy twin pairs from the cohort. Grip strength has been shown to correlate strongly with other muscle groups with respect to strength and power. Men and women were used in this analysis and age was stratified into quartiles in the model. Results further indicated that a large portion of the variance is explained by additive genetic effects and non-shared environmental factors. In addition, there was no significant influence of age or sex in this analysis, indicating that these variables were not confounders or effect modifiers in this study. This heritability estimate is higher than previous data from postmenopausal female twins that indicate a heritability estimate of 30% (6). Other data on strength in older male twins indicated a heritability of 65% at baseline, but when shared environmental factors were included in the model, this estimate dropped to 35% (39). A 10-year follow up indicated a heritability estimate of only 22% (39). More recently, Tiainen et al (274) indicated that handgrip and knee extension strength share a common genetic component, accounting for 14% of the

variance in older female twins. Furthermore, additive genetic effects accounted for 46% of the variance in knee extension strength.

Although there is currently insufficient data to make any definitive conclusions concerning the contribution of heritability to the loss of muscle power with aging, recent evidence suggests that knee extensor strength and power share a common genetic component (274). Data from the Finnish Twin Study on Aging, examined the genetic component of maximal voluntary knee extension power and strength in 101 monozygotic (MZ) and 116 dizygotic (DZ) female twin pairs aged 63 – 76 yr (273). Results indicate that a common genetic factor accounted for 32% of the total variance in leg extensor power and only 4% of the variance in power is attributable to non-shared environmental factors. The results of a 3 year follow-up study reported by the same investigators examined the changes in the contribution of genetic and environmental influences on isometric knee extensor strength and leg extensor power, among 63- to 76-year-old female twins, indicating that the contribution of genetic influences on isometric muscle strength was stable, whereas for leg extensor power the proportion of genetic influences decreased during the follow-up (275). The authors observed new specific environmental effects underlying follow-up muscle strength and power, which effects could be due to the onset of new disease processes or changes in lifestyle.

Additional evidence from twin studies indicate a heritability estimate of .84 for muscle power using a 5s Wingate cycle test (35). Most previous studies have estimated heritability values using standing long jump, vertical jump and distance throws as measures of explosive strength (power). For these measures the estimated

heritability values from twins and siblings 3 through 42 years of age range from 0.14 to 0.91 (169,270). Further these studies revealed that the sex differences in heritability are not as apparent as for strength. Parent offspring data for explosive strength (power) tasks are quite limited, probably reflective of the task demands and age associated decrements in performance on such tasks during adulthood. Thus, many more studies will need to be done in order to more accurately determine the heritability of the explosive type of skeletal muscle power and the heritability of its decline with aging.

Few genome-wide scans or linkage studies have been reported identifying genes or gene regions that may influence muscle phenotypes at baseline or after ST. Chagnon et al.(42) performed a genome-wide search for genes related to body composition and its changes after a 20-wk endurance-exercise training program. These researchers found evidence of significant linkage with changes in FFM and the *IGF1* gene. Huygens et al (123) explored the potential role of the myostatin pathway in relation to muscle strength and estimated muscle CSA in humans using linkage analysis with a candidate gene approach. Linkage patterns were observed between knee extension and flexion peak torque with markers corresponding to the myostatin gene, the *CDKN1A* gene, and the *MYOD1* gene with a maximum LOD score of 2.63 observed with the myostatin gene. Another recent genome-wide linkage analysis study by Karasik et al (137), identified two loci with LOD scores >3.0, shared by leg lean mass with femoral bone geometry on chromosome 12p12.3-12p13.2 and on 14q21.3-22.1. With regards to muscle power, there is a paucity of whole genome linkage analysis studies. The results of one recent study of explorative linkage

analysis showed that the chromosome areas of suggestive linkage for strength and power partly overlapped, with the LOD scores higher than 1.0 being seen for these phenotypes on chromosome 15 (276).

In addition to the genetic influence on muscle phenotypes at baseline, the aforementioned variability of muscle response to a standardized ST protocol suggests that heritability may influence the response of muscle phenotypes to ST, although probably accounting for a smaller percent of the variance. Further evidence for this comes from a study by Thomis et al. (272), in which they investigated the heritability of changes in arm strength after 10 weeks of ST in young male MZ and DZ twins. They observed a genotype by training interaction for one-repetition maximum (1-RM) strength and isometric strength with MZ intra-pair correlations of 0.46 and 0.30, respectively. Twenty percent of the variation in post-training 1-RM strength, isometric strength, and concentric moment at 120 degrees/sec was explained by training-specific genetic factors that were independent from those that explained variation in the pre-training phenotype (30-77%).

Thus, it appears that although genetic factors do account for a proportion of variability in muscle phenotypes at baseline and in response to strength training, the identification of specific contributing genes is complex. A primary strategy is to identify biologically plausible genes and conduct gene association studies, with the ultimate goal of reconciling the complex interplay of genetic and non genetic factors.

Despite the importance of muscle power as an important muscle phenotype especially in the elderly, there are few genetic studies that have studied the influence of specific gene polymorphism on muscle power at baseline or in response to ST in

older adults, with the only exception being Alpha actinin 3 (*ACTN3*) and its premature stop codon at the R577X locus. Several cross sectional studies have shown that the X/X genotype in the ACTN3 gene is significantly less frequent among elite power athletes compared to endurance athletes and to non-athletes (309,310,200,315), suggesting that the X/X genotype is associated with low power. The current research literature on genes influencing power adaptations to ST is extremely scarce. One recent study that examined knee extensor concentric peak power before and after 10-wk ST intervention in 157 older men and women reported that the *ACTN3* R577X polymorphism influences the response of quadriceps muscle power in older adults (59). In this study, in women the X/X carriers exhibited a lower change in relative peak power in response to training compared with the R/R group. In men, the change in absolute peak power in response to training tended to be higher in the R/R group compared with the X/X genotypes.

Further given that muscle power is a complex multi-factorial clinically important phenotype and would be influenced by several genes in several different pathways, identifying the physiologically relevant genes that could influence muscle power at baseline and in response to ST would be useful.

Physiology of *IGF1* promoter polymorphism and the recommendations for future studies.

The *IGF1* gene, that encodes for the IGF-I protein, is located on human chromosome 12 (12q22-q24.1) (189) and consists of 88,066 base pairs. This gene contains two known promoters, six exons, and five introns (262). Depending on the tissue of origin and transcriptional splicing the mRNA typically contains 153 amino

acids and is eventually translated into a 70 amino acid protein with three disulfide bridges (160). The mRNA can produce at least three different transcripts, two of which are expressed in skeletal muscle (176,240,14).

The somatomedin hypothesis came from early experiments trying to understand somatic growth caused by the pituitary gland. Results from these experiments suggested that growth hormone (GH) may be playing a role in somatic growth indirectly by modulating levels of mediating growth factors, designated as somatomedin substance (52,191,243). Insulin-like growth factor-I (IGF-I) was eventually purified from rat serum and shown to be the samotomedin substance regulated by GH (230). It was termed "insulin-like" because of its ability to stimulate glucose uptake into fat and muscle cells, as well as its homology in amino acid sequence with insulin (230). Upon the discovery of IGF-I, the somatomedin hypothesis was further refined to suggest that GH secreted by the pituitary would act on the liver as its target organ, where IGF-I would be secreted to act on bodily tissues causing growth and provide feedback to the pituitary to control the level of GH secretion.

The first indication that the somatomedin hypothesis was incomplete was when D'Ecrole et al (51), discovered that explants of fetal mouse tissue maintained in serum-free media showed higher levels of IGF-I in the culture medium than with extracts of the tissues themselves: i.e., liver, intestine, heart, brain, kidney, and lung. Additional studies supported the finding of various tissues expressing IGF-I, and that this tissue-specific IGF-I could be affected by and also act independent of plasma GH (164,232). However, the direct effect of GH on non-hepatic tissues remained in

question. It was subsequently shown that GH could affect tissues via stimulating local production of IGF-I or act directly on tissues to cause growth (93). The latter process occurred without a mediating factor, but was not as dramatic as when IGF-I was involved in the process.

Action of IGF-I. IGF-I displays numerous diverse functions during both embryonic development and postnatal growth (233). Studies have shown that mice carrying null mutations in the *IGF1* gene are born small and grow poorly postnatally (7). Naturally occurring mutations in the *IGF1* gene are rare. It has been reported that only a single patient, with both intrauterine and postnatal growth retardation has been found who had a deletion of the *IGF1* gene (305). To give a complete description of all the physiological functions of IGF-I are beyond the scope of this review. Therefore a brief background of IGF-I action will be given with specific emphasis on skeletal muscle.

IGF-I exerts some of its influence as an endocrine hormone circulating in the blood stream until reaching its target tissue. Unlike insulin, IGF-I in the circulation is bound by one of six known insulin-like growth factor binding proteins (IGFBPs) (133,135). These binding proteins act as carriers of IGF-I to transport it out of circulation and prolong the half-life by protecting from proteolytic degradation. In addition to their role in circulation, binding proteins are often expressed by target tissues where they act to regulate IGF-I function further. Binding proteins have been shown to augment and attenuate IGF-I action depending on the target tissue (224).

Both gene knockout and transgenic animal studies have demonstrated the importance of IGF-I in muscle development (110,163,47,192,212,307). In muscle,

IGF-1 has been shown to stimulate satellite cell proliferation (43),increase amino acid uptake (177),suppress proteolysis (9), increase thymidine incorporation (85),stimulate myogenic differentiation (78),stimulate myogenesis (247), and enhance DNA accretion and growth (77). Some recent studies have also shown that over-expression of IGF-I exclusively in skeletal muscle prevents EC uncoupling (298) and almost completely maintains skeletal muscle fiber specific force (89) in aged mice. Even though IGF-I will stimulate both proliferation and differentiation of muscle cells in culture (218), unlike other mitogenic factors, it does not stimulate differentiation while it is stimulating proliferation (70). There is a temporal separation between these two effects. This could be due to the versatile intracellular signaling of the IGF-I receptor. IGF-I treatment of muscle cells results initially in a proliferative response during which expression of myogenic factors are inhibited, followed by stimulation of differentiation accompanied by down regulation of proliferative signals (78).

Transgenic mice over expressing the *IGF1* gene show enhanced myotube formation, as well as increased mRNA levels of the myogenic factors, Myo D and myogenin, and elevated mRNA for contractile proteins (47). With a 47-fold increase in IGF-I, these mice showed hypertrophy of all myofiber classes with no increase in body weight or circulating IGF-I (47). In addition, autocrine expression of IGF-I contributes to myotube formation in embryo (103). Autocrine secretion of IGF-I facilitates muscle regeneration after injury in normal and hypophysectomized rats (131,263). *IGF1* mRNA levels and protein levels increase during muscle regeneration (158). Viral mediated over expression of IGF-I in mouse skeletal muscle blocks the age related loss of skeletal muscle mass and strength. Furthermore,

the IGF-I expression prevents significant loss of the fastest and most powerful typeIIb muscle fibers observed in controls (15). Transgenic mice over expressing IGF-I in muscle demonstrate protection from normal loss of muscle mass and strength during aging (192). Additionally, these same transgenic mice display significantly improved muscle regeneration over control mice when muscle damage is induced via cardiotoxin (192). The aged transgenic mice in this study display muscle characteristics similar to or better than younger control mice.

IGF-I is considered important for peripheral nervous system development and the IGF signaling system is considered a potential therapeutic target for the treatment of nerve injury and motor neuron diseases (266). Muscle innervation may be improved in animals over expressing IGF-I. In transgenic mice, skeletal muscle expressing IGF-I prevented aging alterations in the neuromuscular junction, preserved spinal cord motor neuron innervation of muscle, and decreased the loss of type IIb muscle fibers (178). Additionally, Rabinovsky reported that transgenic mice over expressing IGF-I have accelerated muscle and motor neuron regeneration after sciatic nerve crush injury (219). The regeneration or preservation of neural innervation will likely be a causative factor in preventing decline in muscle mass and function with age. Another recent study by Payne et al. (206) demonstrated that induced over expression of IGF-I in spinal cord motor neurons of ageing mice prevents muscle fibre specific force decline, a hallmark of ageing skeletal muscle.

Circulating IGF-I and exercise. IGF-I is produced by various tissues including the skeletal muscle, however, 98% of the circulating form of IGF-I is produced in the liver. Several studies have examined this form of IGF-I in relation to exercise.

Cappon et al. (38) first demonstrated that 10 min of above-lactate threshold cycle ergometer exercise studied in 10 subjects (age 22-35 yr) showed a small, but significant increase in circulating IGF-I levels very briefly after exercise. This increase, however, was evident only until 20 minutes after exercise. Several other studies have also investigated the relation of circulating IGF-I and exercise and have found an acute increase in circulating levels of IGF-I and IGFBP-3 after short-term high intensity dynamic exercise on a bicycle ergometer (11,297,248,65), but many studies failed to demonstrate any acute effect of short term exercise on IGF-I (248,129). This difference may occur because the training intensity, type of training, age and fat mass of the subjects may affect the response of IGF-I to training (135). Nevertheless, ST studies did not show an increase in circulating IGF-I (150,199,202), but did change levels of potential modulators of IGF-1 action, including IGFBP-2, IGFBP-3, and acid labile subunit (202). Other studies have demonstrated an increase in muscle IGF-I and muscle *IGF1* mRNA levels with aerobic training (67,99) and eccentric exercise (10), respectively, but no change in circulating IGF-I levels. Thus, it appears that locally produced IGF-I has an important role in response to exercise in comparison to endocrine-derived IGF-I (294,83). Further evidence for this comes from studies showing that transgenic over expression of IGF-I in skeletal muscles leads to significant hypertrophy without affecting circulating IGF-I levels (47), and mice lacking skeletal muscle IGF-IR have hypoplastic muscles, which in contrast to wild-type littermates are not stimulated by GH treatment (143). A recent study by Mantheny et al.(173) utilized the liver IGF-I-deficient (LID) mouse model, in which the *IGF1* gene was disrupted in the hepatocytes, resulting in ~80% reduction in serum

IGF-I, to stress the importance of locally produced IGF-I. In this study, 12 to 13 month-old male LID and control (L/L) mice were subjected to 16 weeks of resistance training, and it was noted that the changes in the LID mice generally resembled those found in wild-type littermates. Thus, training doubled the lifting capacity and increased hind leg muscle mass, IGF-I mRNA, and IGF-IR phosphorylation. On the basis of these results, the authors concluded that normal muscle performance may be seen even in the setting of severe circulating IGF-I deficiency and that up-regulation of local IGF-I appears to be involved in compensatory growth of muscle in response to resistance training. More surprisingly, the same authors (173) found a reduction in the intracellular signaling of GH, indicating that local increases in IGF-I are in fact GH independent. Although this finding appears controversial, earlier studies in hypophysectomized rats and in rats made GH deficient by treatment with neutralizing GH-releasing hormone antibodies support that muscular IGF-I expression may not be strictly GH dependent (314).

On the basis of the current literature, it appears that the stimulatory impact of exercise on skeletal muscles is mediated by an augmented pituitary GH secretion, leading to an increased local IGF-I synthesis (83). This hypothesis may explain why training studies generally have failed to link an improved muscle performance with changes in circulating IGF-I levels. However, it should be acknowledged that a role of circulating IGF-I cannot completely be ruled out. For instance, patients with GH insensitivity (ÈLaron syndrome) do respond to subcutaneous IGF-I by an increased muscle mass, although the response was less pronounced than the response observed in GH-deficient subjects treated with GH (31).

Thus future research needs to compare circulating versus locally produced IGF-I and their impact on skeletal muscles to elucidate the link between exercise, GH, and muscle hypertrophy. In addition, future studies should investigate the time course for changes in muscle *IGF1* gene expression and protein translation with exercise. Consequently, to gain more information, we need to optimize methodologies for the measurement of tissue IGF-I levels in humans.

Autocrine/paracrine role of IGF-I in aging muscle. Circulating levels of GH and IGF-I, as well as muscle expression levels of IGF-I, decrease with age (292). From 30 to 40 years of age an almost linear decrease is seen with increasing age. Also, in elderly people aged 50-100 years a continued decrease in IGF-I is noted, with roughly 40% decrease by the age of 80. This decline in circulating IGF-I levels is thought to be associated with poor muscle function, impaired physical performance and self reported difficulty in mobility tasks (149,37).

The *IGF1* gene can express multiple isoforms, derived from alternative splicing, depending on the tissue of origin and the stimulus. Alternative splicing is a complex mechanism by which exons are arranged in different combinations from pre-mRNA. It is an important and common process for generating protein diversity and regulating gene expression in higher eukaryotes. The predominant circulating isoform of IGF-I, produced by the liver due to GH stimulation, has been termed IGF-1Eb and is produced by splicing out exon one and thus utilizes the exon two promoter. This isoform is predominantly expressed in the liver, and its role in muscle is mostly unknown.

The muscle expresses two known isoforms of the *IGF1* gene when it is subjected to stretch or mechanical stimulation. The first muscle isoform is termed IGF-1Ea (240). Several different abbreviations have emerged for this isoform: L.IGF-1 and m.IGF-1 (100). This isoform is initiated at the exon 1 promoter similar to the liver form, yet in 1 Ea, exon 5 is removed by alternative splicing. Transgenic mice that over-express this isoform in skeletal muscle have been shown to have marked hypertrophy (192). Additionally, older animals showed signs of protection against the normal loss of muscle mass associated with aging (192). It was concluded that the over-expression of this isoform of IGF-I preserved muscle architecture and age-independent regenerative capacity of muscle.

The second IGF1 isoform expressed in muscle, termed mechano-growth factor (MGF) or IGF-1Ec, is a splice variant resulting from a novel splice acceptor site in the intron preceding exon 6 and is generated in muscle subjected to stretch and overload (311). Structurally, the MGF mRNA differs from its liver counterpart because of the presence of a 49-base pair insert on the carboxyl end of the protein, which is derived from exon 5 of the *IGF1* gene. This isoform is not glycosylated, therefore, it is expected to have a shorter half-life than the liver IGFs and is therefore likely to be designed to act in an autocrine/paracrine, rather than in a systematic fashion. As a result, it binds to its own muscle-specific binding protein, in the interstitial tissue spaces. Animal studies have shown significant up regulation of MGF with muscle stimulation (176,311). Other studies have shown that locally produced IGF-I can stimulate muscle hypertrophy through activation of satellite cells and increased protein synthesis rates (1,115,253,312,203,174). Several human

studies have shown an increase in muscle IGF-I with a single bout of resistance exercise (10,258,216). However, attenuation of MGF induction has been observed in aged human muscle after resistance exercise (102). Thus, it has been postulated that sarcopenia may in part be due to failure to generate an isoform of IGF-I that is necessary to initiate the remodeling of muscle, i.e. to stimulate satellite cell activation and proliferation (87,88). Barton et al. (14) recently expanded on this concept by showing that adeno-associated virus expression of IGF-I Ea and Eb promoted muscle growth in 2-4 month old rats, whereas in 6-month old rats, IGF-I Ea was an effective hypertrophic agent but IGF-I Eb was not. These results suggested that the ability to accumulate Eb was attenuated with increased age of the rat or that there was age associated resistance to Eb. However, Hameed et al. did report ~170% increase in MGF with 5 weeks of ST and no increases in circulating IGF-I in elderly men.

Results from previous studies clearly show that ST induces local expression of IGF-I and it is likely that IGF-I is mediating many of the hypertrophic effects observed in skeletal muscle. Yet as previously mentioned, there is significant variability seen in the strength and hypertrophic response of muscle to ST. Additionally, the increases in *IGF1* mRNA that occur in response to resistance exercise have been shown to range from 2-864% (102), and a variation for IGF-I increase with ST of ~137% has been observed in the elderly (258,101). These results suggest that genetics could be affecting this response. Indeed, studies have shown that circulating levels of IGF-I are almost completely under genetic control in healthy twin children and the variability in circulating levels in the elderly is estimated to be ~ 63% under genetic control (116,136). We could not find any studies that have

examined the heritability of *IGF1* muscle expression. An autosomal genome wide search for genes related to fat free mass (FFM) and its changes after exercise training revealed that a polymorphism in the *IGF1* promoter region displayed significant linkage with changes in FFM (42). Additionally, this same polymorphism was shown to be associated and in linkage with baseline FFM and with the change in FFM resulting from aerobic exercise training (267). More recently, this polymorphism has been shown to be associated with change in muscle strength and muscle quality with ST in older men and women (147,104).

IGF1 CA dinucleotide repeat polymorphism. The *IGF1* polymorphism identified in the genome wide scan and most association studies is the CA dinucleotide repeat polymorphism near the promoter region of the *IGF1* gene in humans (299). A similar CA repeat near a gene promoter has been shown to alter gene expression in rats and humans (2,239). Repeat sequences account for at least 50% of the entire human genome sequence. Commonly defined as a perfect or near- perfect sequence repeat of 1-5 bases, microsatellites are found in tandem repeat units of 10-30 repeats. Alternating purine-pyrimidine nucleotides (i.e. CA) are one type of microsatellite and, other than SNP's, microsatellites are the most variable component of the human genome. Three percent of the human genome consists of microsatellite repeats of which CA dinucleotides are the most common making up 0.5% of the human genome (152). The biological function of repeat units has not been completely defined but a non-random distribution of repeats exists in the human genome suggesting an evolutionary importance.

A proposed function of some microsatellites is to regulate gene transcription. A disproportionate amount of these repeats are found in the promoter regions of genes in the human genome (249). This along with their known ability to alter gene transcription and the binding affinity of nuclear transcription factors make them areas of likely functional importance (139). Alternating purine-pyramidine microsatellites in promoter regions have been reported to be involved in regulation of gene expression (138,196,249). Khashnobish et al. (142) were the first to report *in vivo* regulation of gene expression by a CA repeat unit of varying lengths in Podospora anserine. Their results demonstrated that the number of CA repeats positively affects gene expression. In a study by Peter et al. (209), it was shown *in vitro* that a CA repeat polymorphism commonly found in the human population can affect gene expression depending on the length. This was the first study to show that microsatellite length polymorphisms that are commonly found in normal human population can alter gene expression. Furthermore, they demonstrated that the CA repeat element might serve as a binding site for specific nuclear regulatory proteins. Regulation of gene expression by varying of CA repeats in the promoter region, as mentioned, or in introns has been shown to affect gene expression in rats and humans (2,45,239).

The microsatellite polymorphism near the promoter region of the *IGF1* gene is typically between 16 and 22 CA repeats and this polymorphism is commonly referred to by the base pair length of the amplified DNA fragment (e.g. 192 bp). The 192 allele (19 CA repeats at nucleotide position 1087-1127 in the human *IGF1* DNA sequence Genbank accession number AY260957, RS# 10665874) of the *IGF1*

promoter polymorphism has been investigated in various contexts. Genotyping of this polymorphism is typically separated into three groups: 192 homozygotes, 192 heterozygotes, and non-carriers of the 192 allele. It has not been determined whether the 192 polymorphism is causally related to changes in *IGF1* function, yet, the 192 allele is the most prevalent allele in the majority of the populations studied to date. A study by Vaessen et al. (288) reported that in a population-based sample, 88.4% of the subjects were homozygous or heterozygous for the 192-bp allele, suggesting that this the wild-type allele from which all other alleles originated. Although this polymorphism has not been proven to be functional, it has been proven to be a potential marker for disease-related phenotypes and possibly *IGF1* expression levels, as well as it has been previously shown to influence muscle strength and muscle quality in response to ST in older individuals (147,104).

Rosen et al. (236) first implicated this polymorphism with serum levels of IGF-I and bone mineral density in a study examining older men and women. It was reported that 192 homozygotes had lower blood levels of IGF-I and in a group of older men,192 homozygotes made up a disproportionately large percentage of those with idiopathic osteoporosis (236). Since this report other groups have investigated the influence of the 192 allele on circulating IGF-I levels with some studies showing decreased (80,229), increased (144,183,231,288), or no difference unless combined with oral contraceptive use (132,313). There have been other additional reports of the 192 allele showing no association with IGF-I blood levels or any measured phenotype (4,56). The study by Delellis et al. (56), examined 250 adult women for association of the *IGF1* microsatellite and breast cancer risk, while the report from Allen et al. (4)

examined older and younger men for association of blood levels of IGF-I and the *IGF1* microsatellite polymorphism. It was concluded by these studies that the 192 polymorphism is unlikely to be associated with *IGF1* function. In contrast a more recent study in 163 premenopausal women, reported that the number of 19 alleles at the 5' polymorphism was associated with lower circulating levels of IGF-I (P = 0.02) and explained 5% of the variance in IGF-I levels (71). Similarly, recently Hoyo et al.(118) conducted a study to determine the predictors of serum IGF-I and IGFBP3 levels and the results revealed that in African-americans, 17% of the variation in serum IGF-I levels were explained by cigarette smoking and carrying the *IGF1* $(CA)_{19}$ repeat allele.

If the 192 allele itself is not functional it would at least seem to be a valid marker for phenotypes related to IGF-I expression. The possibility exists that the 192 polymorphism is in linkage disequilibrium with a functional polymorphism in the *IGF1* gene. Currently there are very few studies that have examined this polymorphism in relation to skeletal muscle phenotypes, with none that has examined its association with muscle power. Due to the substantial loss of muscle power and IGF-I expression with advancing age and the close association between muscle power and performance of functional abilities, this association in older adults could have important clinical significance.

Although results are inconclusive for the effect of the 192 polymorphism on IGF-I levels, it seems possible that the *IGF1* 192 polymorphism may affect skeletal muscle-related phenotypes because of previous results showing positive associations of this polymorphism with FFM (267,42) and the change in muscle strength and muscle

quality with ST (147,104). However, in all studies reported, the association was studied between this polymorphism and total IGF-I in circulation. Considering that circulating IGF-I levels may not reflect the IGF-I levels present locally in skeletal muscle tissue, future studies should study the relation of this polymorphism with transcription and protein levels of *IGF1* in the muscle, to better understand the functionality of this polymorphism in relation to skeletal muscle.

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