ABSTRACT

Title of Document: ADRENERGIC RECEPTOR(ADR) GENOTYPE INFLUENCES THE EFFECTS OF STRENGTH TRAINING ON MID-THIGH INTERMUSCULAR FAT

Lili Yao, Doctor of Philosophy, 2006

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Sarcopenia results in an increase in intermuscular fat (IMF) and low density muscle (LDM), which is associated with adverse health and functional consequences. Although strength training (ST) is considered an intervention of choice for the prevention and treatment of sarcopenia, little is known about its effect on IMF or LDM. Regional fat alterations resulting from exercise interventions may be influenced by adrenergic receptor (ADR) β2 Gln27Glu and ADRα2b Glu^{12}/Glu^{9} gene polymorphisms. To examine the influence of this polymorphism on mid-thigh IMF, LDM and normal density muscle (NDM), we studied 46 older men and 52 older women before and after a 10-week single leg knee extension strength training (ST) program. The ST program resulted in a substantial increase in one-repetition maximum (1-RM) strength (P = 0.0001) and NDM (P = 0.0001), but no significant

changes in IMF and LDM in the whole group. However, IMF was significantly reduced with ST in subjects carrying ADRβ2 Glu27 (-2.3 cm^2, P = 0.028), but no significant change was observed with ADRβ2 Glu27 noncarriers (+1.5 cm^2, P = 0.14). The decrease in IMF in those with the ADRα2b Glu^9 allele was approaching significance (-1.9 cm^2, P = 0.066), and significantly different (-2.9 cm^2, P = 0.043) from a nonsignificant increase in IMF in the ADRα2b Glu^9 allele noncarriers. ADRβ2 Glu27 carriers who also carried the ADRα2b Glu^9 allele experienced a significant loss of IMF with ST (-3.8 cm^2 ± 1.6, P = 0.018). These results suggest that the response of IMF to ST is influenced by ADRβ2 Gln27Glu and ADRα2b Glu^{12}/Glu^9 polymorphisms.

ADRENERGIC RECEPTOR (ADR) GENOTYPE INFLUENCES THE EFFECTS OF STRENGTH TRAINING ON MID-THIGH INTERMUSCULAR FAT.

By

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INTRODUCTION

Sarcopenia is the age-associated loss of muscle mass and strength. These losses are also associated with a deterioration in health status and with adverse effects on functional abilities in the elderly (1). Aging adversely affects the quality, as well as the quantity, of skeletal muscle (SM). For example, in African American women, fat infiltration of muscle increases with age (2), leading to the accumulation of intermuscular fat (IMF) and the development of low density muscle (LDM). Elevated levels of thigh IMF have been linked to insulin resistance in muscle and to the development of type 2 diabetes (3, 4). In addition, higher LDM is associated with lower muscle strength (5), with poorer leg function (6) and with greater incidence of mobility limitations in the elderly (7).

Despite this relationship of limb IMF and LDM to health and functional status and that ST is now commonly prescribed for the prevention and treatment of sarcopenia (8), little or no information is available on the effects of ST on limb IMF or LDM. In this regard, Sipila et al. (9) reported a reduced percent of thigh IMF in response to ST, but no information on absolute IMF change was provided. The reduced percentage of fat may have just been due to the increase in thigh muscle mass, which lowers the percent of fat tissue, even if the total mass of fat doesn't change. One study showed that the combination of ST with aerobic exercise training decreased LDM (10) and another study showed that ST together with a low-calorie diet reduced thigh IMF (11). Unfortunately, neither of these two studies can tell us the independent effects of ST on IMF or LDM. Thus, the first purpose of this study was to examine the effects of ST on IMF and LDM.

ST has been showed to increase sympathetic nerve activity (12). Norepinephrine (NE) derived from sympathetic nerves regulates lipolysis by binding to stimulatory adrenergic receptors (ADR) (β1, 2, or 3), mainly ADRβ2 in skeletal muscle (13), and inhibitory ADRα2b receptors. The balance between ADRβ2 and ADRα2b can thus determine the relative efficacy of NE as a lipolytic hormone. ADRβ2 Gln27Glu polymorphisms have been associated with fat adaptation to exercise training in some (14, 15), but not all studies (16). The combined effects of ADRβ2 Gln27Glu and ADRα2b Glu^{12}/Glu^{9} polymorphisms on the total body fat reduction induced by aerobic exercise training (15). However, studies investigating genotype influences of ST effects on fat phenotypes are unavailable. Thus, the second purpose of this study was to investigate ADR genotype influences on IMF and LDM responses to ST. We hypothesized that ST will significantly reduce IMF and LDM, and ADRβ2 and ADRα2b gene variants will significantly influence these effects.

METHODS

Subjects

Ninety-eight relatively healthy, sedentary, Caucasian (n = 67) and African American (n = 31) men (n = 46) and women (n =52) aged 50-85 years served as subjects for this study. All subjects underwent a phone-screening interview, received medical clearance from their primary care physician and completed a detailed medical history prior to participation. They 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, which was 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 study, and body weight was measured weekly throughout the study to help confirm compliance to maintaining a stable diet.

Genotyping

Genomic DNA was prepared from EDTA-anticoagulated whole blood samples by standard salting-out procedures (Puregene DNA Extraction, Gentra systems Inc). A restriction fragment length polymorphism (RFLP) procedure (17) was used to genotype for ADRβ2 Gln27Glu polymorphism using Fnu4H restriction enzyme.

ADRα2b polymorphisms were analyzed directly on 3% agarose gel for 3 hours at 100 V for maximum separation and clarity. The genotype procedures were validated by direct sequencing of a random collection of samples.

Body composition assessment

Body composition was estimated 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. Hologic version 8.21 software for tissue area assessment was used to analyze for total body fat-free mass (FFM), fat mass, and % fat. 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 CV was 0.6 % for FFM and 1.0% for % fat.

CT of the Mid-thigh

An axial computed tomography (CT) imaging of the trained and untrained mid-thighs was obtained (GE Lightspeed Qxi, General Electric, Milwaukee) at baseline and during the last week of the 10-week unilateral ST program. Mid-thigh was defined as mid-point of the most distal point of the ischial tuberosity to the most proximal part of the patella, while subjects were in a supine position. Section thickness was set at 10 mm, with 40 mm separating each section, based on previous work in our laboratory with slight modifications (18). 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 were used to obtain a pixel resolution of 0.94 mm. CT scans were analyzed using the Medical Image Processing, Analysis, and Visualization (MIPAV) area assessment program (NIH, Bethesda). Briefly, IMF was distinguished from the subcutaneous adipose tissue by manual drawing of a line along the deep fascial plane surrounding the thigh muscles. IMF was then segmented into a separate image, in which the IMF, LDM and normal density muscle (NDM) were identified based on Hounsfield Units (HU) as follows: IMF = –190 to –30, LDM = 0 to 30, and NDM = 31 to 100, as previously described (4, 19). Bone marrow adipose tissue area was excluded in the analyses. The technician was blinded to subject identification, date of scan, and training status, for both baseline and after training scans. Reproducibility of IMF, LDM and NDM was assessed by repeating the analysis of 12 CT scans 5 times performed on 5 separate days and showed a coefficient of variation of less than 5% for all three components.

Strength testing

One-repetition maximum (1 RM) strength tests were assessed before and after the ST program using the same type of air-powered knee-extension resistance machine (Keiser Sports/Health Equip. Co., Inc., Fresno, CA) as was used in training as described previously (12). The same investigator conducted strength tests for each subject both before and after training using standardized procedures with consistency of seat adjustment, body position, and level of vocal encouragement. All subjects were positioned with a pelvis strap (seat belt) to minimize the involvement of other muscle groups. The 1 RM was achieved by gradually increasing the resistance after

each successful repetition from an estimated sub-maximal load until the maximal load was obtained. A customized light system was used to assure that each attempted exercise trial achieved an appropriate range of knee extension.

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. The untrained control leg was kept in a relaxed position throughout the training program. 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, as described by Delmonico et al.(20). We did not have those ≥ 75 yrs perform the last set out of 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 (21). The protocol was designed to elicit near maximal effort on every repetition, while maintaining a relatively high training volume.

Statistical analysis

ADRβ2 Gln27Glu and ADRα2b Glu^{12}/Glu^{9} genotype distribution was evaluated for conformity with Hardy-Weinberg equilibrium using chi-square test with one degree of freedom. Changes in total body mass, FFM, body fat, percent body fat and 1 RM were tested using paired t-test. The influences of genotypes on the ST – induced effects on IMF, LDM and NDM were determined by analysis of covariance

(ANCOVA). The change in IMF, LDM and NDM was calculated by subtracting the difference between the changes (pre- to post-training) of the untrained leg from the change (pre- to post-training) of the trained leg. The ADRβ2 polymorphism was categorized as Glu27 carriers (Gln27Glu and Glu27Glu) and Glu27 noncarriers (Gln27Gln); The ADRα2b polymorphism was categorized as Glu^{9} carriers (Glu^{12} / Glu^{9} and Glu9 / Glu^{9}) and Glu^{9} noncarriers (Glu^{12} / Glu^{12}). The initial linear model included the two genotype groups, sex and ethnicity as class variables, while age, change in body fat and baseline values were covaried for IMF, change in NDM were additionally covaried for LDM. The model for NDM covaried age and baseline values only. The models also included selected two and three factor interactions. Non-significant sources of variation were deleted, one at a time, starting with the least significant higher order source. The significance was set as $P < 0.05$. All means were adjusted to the mean age (63 years), and weighted for gender-hormone replacement (7% female, hormone replacement, 46% female, non-replacement and 47% males), ethnicity (68% Caucasian and 32% African American) and genotype distributions (48% Glu27 carriers and 52% Glu27 noncarriers; 48% Glu^{9} carriers and 52% Glu^{9} noncarriers). In addition, IMF means were also adjusted to change in body fat (-180 gram) and corrected for baseline (trained minus untrained) IMF (-0.41 cm^2); LDM means were also adjusted to change in body fat (-180 g) and change in NDM (19.34 cm^2), and corrected for baseline LDM (1.65 cm^2); NDM means were corrected for baseline NDM (9.1 cm^2).

RESULTS

Subjects characteristics

The physical characteristics of subjects at baseline and after training for men (n = 46) and women (n = 52) are shown in Table 1. Men significantly increased their FFM and total body mass, whereas, women showed no significant change in FFM or total body mass in response to ST. There was no significant change in body fat or percent body fat in either men or women with ST. The 1-RM strength values increased by 28.4 % in men (+9.1 kg, P = 0.0001) and 27.8% in women (+5.2 kg, P = 0.0001).

Genotype

The genotype frequencies and sample sizes for the ADR alleles and genotypes are shown in Table 2. ADRα2b Glu^{12}/Glu^{9} and ADRβ2 Gln27Glu allele frequencies were comparable to those reported previously (15), and fit the expectation of Hardy-Weinberg equilibrium for each polymorphism (Gln27Glu, $\chi^2 = 0.07$, P = 0.97; Glu^{12}/Glu^{9}, $\chi^2 = 0.36$, P = 0.84).

IMF, LDM and NDM

IMF was not significantly changed with ST in the whole group (0.35 ± 0.68, P = 0.6114). There were significant training-induced reductions in IMF in the ADRβ2 Glu27 carriers (-2.3 cm^2, P = 0.028; Figure 1), but no significant change in IMF in Glu27 noncarriers. The training-induced reduction in IMF in the ADRα2b Glu^{9} carriers approached significance (-1.9 cm^2, P = 0.066; Figure 2), whereas ADRα2b Glu^{9} noncarriers did not experience significant changes in IMF with ST. The decrease

in IMF in the ADRβ2 Glu27 carriers with training was significantly different (-3.8 ± 1.5, P = 0.014) from the non significant IMF change in the ADRβ2 Glu27 noncarriers. The change in IMF responses to ST in ADRα2b Glu^9 carriers was significantly different (-3.0 ± 1.4, P = 0.043) from the change in IMF in the ADRα2b Glu^9 noncarriers.

Carriers of ADRβ2 Glu27 who also carry ADRα2b Glu^9 alleles (Glu27 + / Glu^9 +) showed a significant decrease in IMF with ST (-3.8 cm^2, P = 0.018; Figure 3), while carriers of neither ADRβ2 Glu27 nor ADRα2b Glu^9 alleles (Glu27 – / Glu^9 –) showed a significant increase (+3.0 cm^2, P = 0.046) in IMF. The change of IMF in Glu27 + / Glu^9 + carriers was significantly different (-6.8 ± 2.3 cm^2, P = 0.020) from Glu27 – / Glu^9 – carriers. Other allelic combinations (ADRβ2 Glu27 + / ADRα2b Glu^9 – or ADRβ2 Glu27 – / ADRα2b Glu^9 +) showed no significant change in IMF with ST and there were no significant differences with other genotypes combined.

LDM was not significantly changed with ST (-1.35 ± 0.78, P = 0.09). However, there was a significant ADRα2b genotype by change in NDM interaction effect on LDM response to ST (P = 0.0215). Thus, the effect of ADRα2b on LDM was dependent on size of the change in NDM with ST. The increase in NDM was consistent for all genotypes with ST (19.3 ± 2.2 cm^2, P = 0.0001), when adjusted for ethnicity, sex, age and baseline value.

DISCUSSION

To our knowledge, this is the first study to examine the effects of ST and the influence of ADR genotypes on IMF and LDM. These results support our hypothesis that ADR genotypes influence the responses of IMF to ST, but do not support our hypothesis of a similar influence on LDM response to ST, or on a reduction of IMF and LDM with ST, independent of genotype. The data demonstrate that ST reduces IMF in those who are ADRβ2 Glu27 carriers, but not in those who are Glu27 noncarriers. In addition, Glu27 carriers who also carried ADRα2b Glu^9 alleles, showed a significant decrease in IMF with ST, which was significantly different from those who carry neither ADRβ2 Glu27 alleles nor ADRα2b Glu^9 alleles.

It has been reported that ST decreases both total and regional fat (22), including intra-abdominal fat (23). Adrenergic receptors (ADR), especially ADRβ2, have been shown to play a major role in triglyceride lipolysis in adipose tissue and skeletal muscle (13). Moreover, polymorphisms of the ADR gene have been associated with adipose tissue deposition and catabolism (24, 25). In this context, ADR genotypes may influence exercise training-induced fat reductions. For example, Phares et al.(15) reported a greater loss in total % fat and in trunk fat in ADRβ2 Glu27 carriers than in noncarriers, in response to aerobic exercise training. In addition, ADRα2b Glu^9 noncarriers who also carried ADRβ2 Glu27 lost greater fat mass than noncarriers of either variant in their study. The results of the current study extend the results of Phares et al. (15) to ST by showing that ST-induced reductions in regional fat (IMF) is similarly influenced by the ADRβ2 Gln27Glu polymorphism, such that

Glu27 carriers respond to training by reducing IMF, whereas, noncarriers do not, in middle-aged and older adults.

Maintaining low levels of muscle fat is important for the elderly because of its association with metabolic disorders and functional disabilities (4-7). Nevertheless, it cannot be determined from these studies whether the magnitude of IMF loss with ST in the present study is enough to result in improved function or metabolic state. However, these results do suggest that reversing some of the age related muscle loss is not the only potential value of ST as an intervention for sarcopenia, at least for those of a specific genotype (e.g., carriers of ADRβ2 Glu27 allele alone or together with ADRα2b Glu^9).

It is unclear why the ST program did not result in a significant reduction in IMF and LDM in the entire group, independent of genotype. There are several possible explanations. First, this is likely due to the significant increase in Glu27 – / Glu^9 – carriers. Second, the energy expenditure of our training program was likely too low to account for a significant loss in regional or total body fat in the group as a whole. Only a single exercise that incorporates a single muscle group was used. Although multiple sets of this exercise were performed, the total exercise time, when you exclude rest periods, was less than 5 minutes, which accounts for a low energy expenditure training protocol. Third, this type of heavy resistance, short duration exercise uses anaerobic metabolism as the primary energy pathways (26). Although increased intramuscular lipid oxidation has been observed in electrically induced contraction of isolated skeletal muscle (27) and after 5 hours of continuous knee

extensor exercise (28), these studies used a very different experimental stimulus than was used in the present investigation.

However, despite no significant change in total body fat and the use of low energy expenditure and a primarily anaerobic exercise regime, we found significant ST - induced reductions in mid-thigh IMF in those subjects who either carry the ADRβ2 Glu27 allele alone or both ADRβ2 Glu27 and ADRα2b Glu^9 alleles. In this regard, Green et al (29) reported that the presence of the Glu27 allele is protective against the agonist – induced decreases in ADRβ2 expression, although other studies claimed the opposite for receptor functions (30). Based on the Green et al (29) study, we postulated that Glu27 allele carriers may have more ADRβ2 receptors than Glu27 allele noncarriers in response to ST-induced catecholamine stimulation, thereby resulting in more hydrolysis of triglyceride in IMF. Small et al (31) reported that the presence of Glu^9 resulted in a decreased inhibition of adenyle cyclase (AC) by ADRα2b. Thus, we postulated that the presence of Glu^9 favors lipolysis stimulated by ADRβ2, resulting in a greater likelihood of significant reductions in IMF in those who carry both Glu27 and Glu^9 alleles. Nevertheless, lipolysis is not a perfect predictor of fat loss because FFAs released from lipolysis can be reesterified back to triglyceride if not oxidized by muscle. Thus, fatty acid oxidation becomes an important part of the explanation for exercise training-induced fat loss, which will require further study.

To control for biological, seasonal and methodological variations, investigators have used a no exercise control group (9). However, a no exercise control group cannot control for genetic differences between the two groups, attention effects due to

the training group receiving more attention than the control group, or the many differences resulting from group heterogeneity. Therefore, we have recommended unilateral limb training, using the untrained limb as a control, to isolate the independent effects of ST (32).

However, there were limitations of the present study. First, although our sample size is considered relatively large when compared to previously published ST studies, it is small for genotype comparisons. Therefore, we limited our comparisons to Glu27 carriers vs Glu27 allele noncarriers, instead of comparing all three genotype groups, to achieve our 80% criterion for statistical power. Second, the age range of subjects in this study was quite large (50 to 83 years). However, we did covary for age in our analysis to account for this heterogeneous age group. Third, training was restricted to the quadriceps muscle group, yet a portion of the fat measured fell into the adjoining hamstrings muscle group. In addition, it has been estimated that ~50% of the FFA oxidized during exercise comes from the general circulation (33, 34). Therefore, the reduction of thigh IMF with ST in the ADRβ2 Glu27 carriers could possibly be accompanied by reductions of fat in other regions, not measured in this study. It is likely, however, that other regions did not experience significant fat reductions, given that there was no significant reduction in total body fat, subjects were constantly reminded not to change their usual caloric intake, were weighed weekly to assure compliance, and the caloric expenditure of the training protocol was low. Finally, although the inclusion of seven women who were taking hormone replacement medication in this study should be considered a limitation, we included these women as a separate group in the statistical analysis and there were no significant differences

in IMF response to ST between the seven women who were taking medication and those who were not.

In conclusion, this is the first study to report that ADR genotype can influence the effects of ST on intermuscular fat in middle-aged and older adults. The data indicate that those who carry the ADRβ2 Glu27 allele alone or with ADRα2b Glu^9 allele experience a reduction in intermuscular fat as a result of strength training. The results of the present study also provide support for new hypotheses to investigate other gene polymorphisms, such as ADRβ3, larger scale investigations, and to examine functional or metabolic changes associated with the ST-induced reductions in intermuscular fat.

Table1. Physical Characteristics at Baseline and After Strength Training (ST)

	Baseline	After ST
Men (n = 46)		
Age (years)	64.4 ± 1.2	
Height (cm)	173.8 ± 1.0	----
Total body mass (kg)	84.0 ± 1.8	84.5 ± 1.9*
Body fat (kg)	23.4 ± 1.0	23.3 ± 1.0
Percent body fat (%)	27.4 ± 0.8	27.2 ± 0.7
FFM (kg)	60.6 ± 1.1	61.2 ± 1.1**
1-RM (Kg) ‡	32.4 ± 1.2	41.5 ± 1.6**
Women (n = 52)		
Age (years)	62.7 ± 1.2	
Height (cm)	162.5 ± 0.8	----
Total body mass(kg)	73.2 ± 1.7	73.3 ± 1.8
Body fat (kg)	28.9 ± 1.1	28.7 ± 1.1
Percent body fat (%)	38.8 ± 0.7	38.5 ± 0.7
FFM (kg)	44.3 ± 0.7	44.6 ± 0.8
1-RM (Kg) ‡	18.7 ± 1.0	23.9 ± 1.0**

Values are mean ± standard error. FFM: fat free mass

1 RM: one repetition maximum

* $P < 0.05$, * * $P < 0.01$

‡ There were two women and one man who had missing 1 RM data.

Table 2. Adrenergic Receptor (ADR) Gene Polymorphisms: Allele and Genotype Frequencies and Sample Sizes.

ADR gene polymorphisms alleles and genotypes	Frequency	Sample Size
ADRα2b Glu^{12}	0.73	-
ADRα2b Glu^{9}	0.27	-
ADRα2b Glu^{12}/Glu^{12}	0.52	51
Glu^{12}/Glu^{9}	0.42	41
Glu^{9}/Glu^{9}	0.06	6
ADRβ2 Gln27	0.72	-
ADRβ2 Glu27	0.28	-
ADRβ2 Gln/Gln	0.52	51
Gln/Glu	0.41	40
Glu/Glu	0.07	7

Figure Captions

Figure 1. Change of intermuscular fat (IMF) with ST in adrenergic receptor (ADR) β2 Glu27 carriers and noncarriers. P values connecting two bars represent tests of differences between genotypes and p values associated with a single bar represents change due to training effects in the designated genotype group. All other differences and changes were non significant. .

Figure 2. Change of intermuscular fat (IMF) with ST in adrenergic receptor (ADR) α2b Glu^{9} carriers and noncarriers. P values connecting two bars represent tests of differences between genotype groups and p values associated with a single bar represent changes due to training effects in the designated genotype group. All other differences and changes were non significant.

Figure 3. Change of intermuscular fat (IMF) with ST in carriers of adrenergic receptor (ADR) β2 Gln27Glu and ADRα2b Glu^{12} / Glu^{9} polymorphisms combined. P values connecting two bars represent tests of differences between designated genotype groups and p values associated with a single bar represent changes due to training effects for the designated genotype group. All other differences and changes were non significant.

Figure 1.

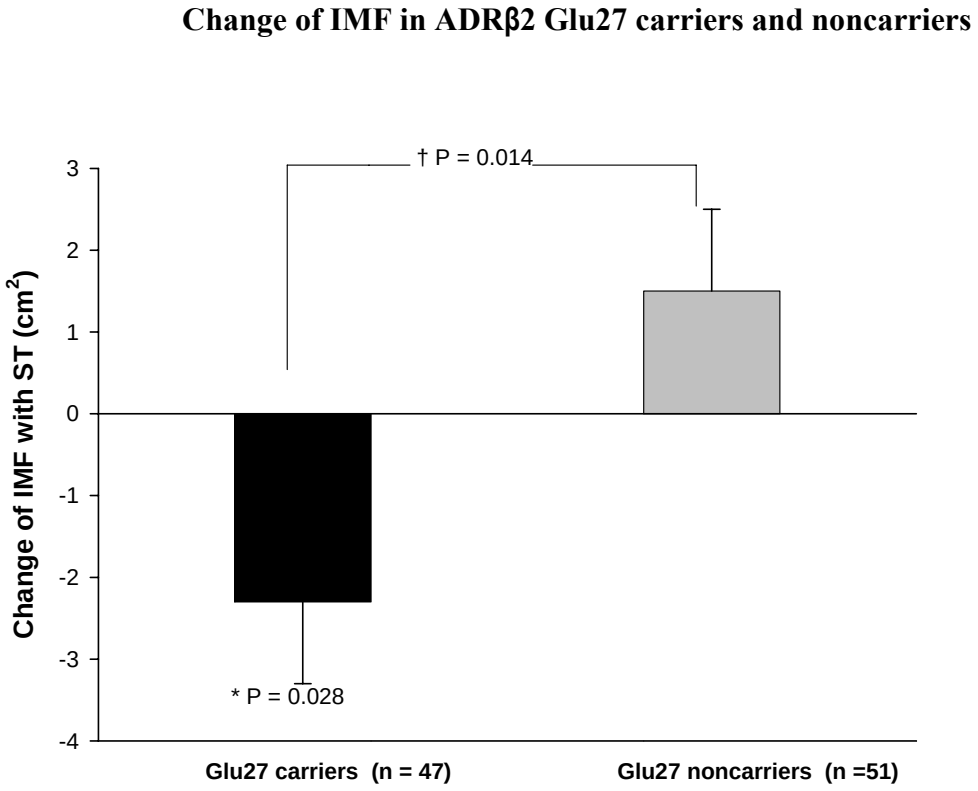

Change of IMF in ADRβ2 Glu27 carriers and noncarriers
† P = 0.014
* P = 0.028
Change of IMF with ST (cm²)
3
2
1
0
-1
-2
-3
-4
Glu27 carriers (n = 47)
Glu27 noncarriers (n =51)

Figure 2.

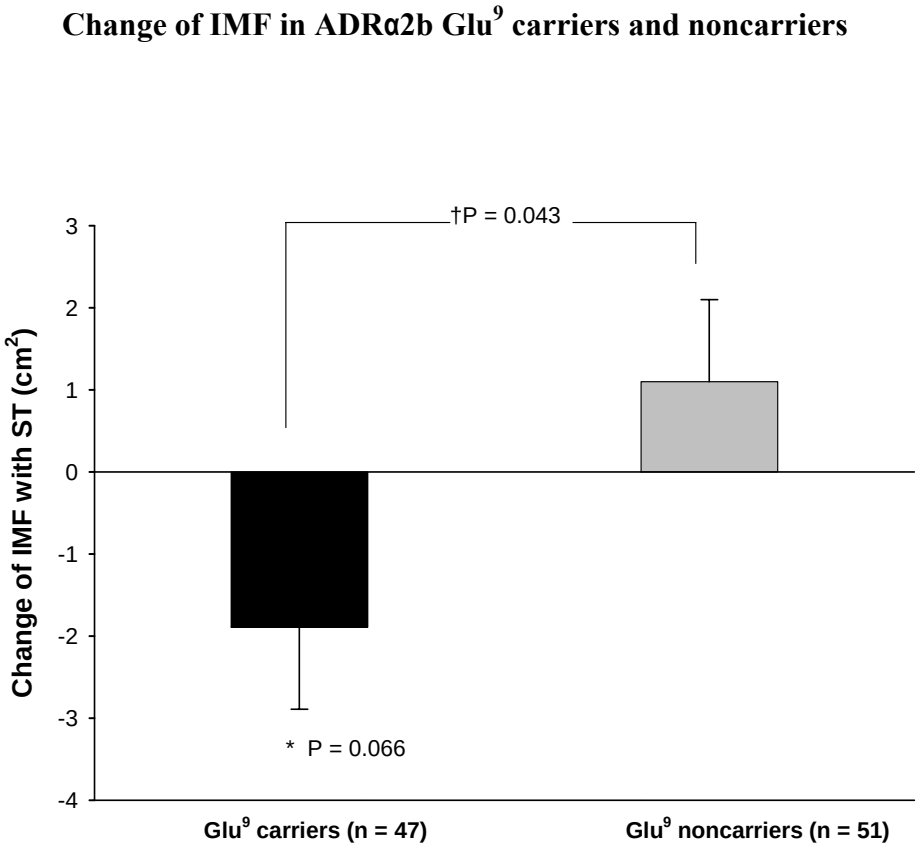
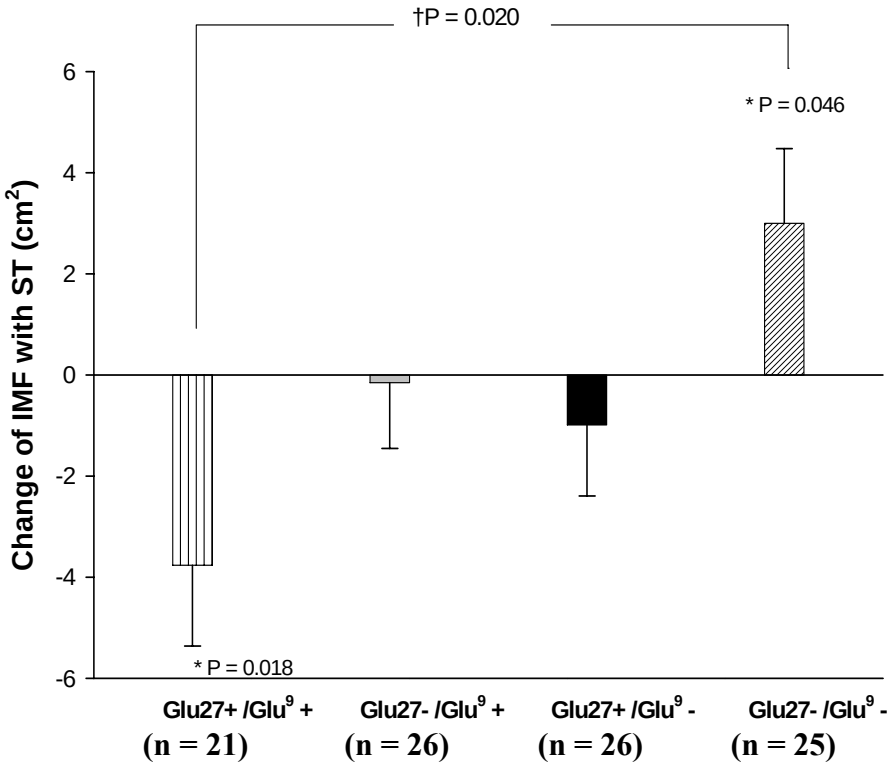

Change of IMF in ADRα2b Glu9 carriers and noncarriers
†P = 0.043
3
2
1
0
-1
-2
-3
-4
Change of IMF with ST (cm2)
* P = 0.066
Glu9 carriers (n = 47)
Glu9 noncarriers (n = 51)

Figure 3.

Change of IMF in carriers of ADRβ2 and ADRα2b genotypes combined



APPENDIX A

Research Hypotheses

1. IMF and LDM will be reduced after 10 weeks of ST, independent of genotypes, gender and ethnicity.
2. ADRβ2 Glu27 allele carriers will lose more IMF or LDM than noncarriers in response to ST
3. ADRα2b Glu^{9} allele carriers will lose less IMF or LDM than noncarriers in response to ST.

Delimitations

1. The scope of this study will be delimited to 98 men and women between the ages of 50 and 81 yrs who volunteer as study participants.
2. Participation in the study will be limited to healthy participants free of musculoskeletal or cardiovascular disease.
3. Based on previous research, subjects will be divided into three groups in determining the effect of ADRβ2 and ADRα2b, respectively. The groupings will be based on homo and heterozygosity for the ADRβ2 Gln27Glu or ADRα2b Glu^{12}/Glu^{9} polymorphism.

Limitations

1. The participants will not be randomly selected from the general population, but volunteers. Therefore, the results of this study cannot be generalized to

individuals who do not possess characteristics such as age, body size, physical activity, etc. similar to those of subjects in the study.

2. Many factors related to health and lifestyle such as dietary habits, physical activity habits, medication regimens, and medical conditions will be reported by subjects. Because the accuracy of these reports cannot be verified, it is possible the results of this study could be adversely affected if inaccurate self-reports occur.
3. 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).
4. Genotypes other ADRβ2 Gln27Glu and ADRα2b Glu^{12}/Glu^{9} polymorphisms will not be assessed in the proposed study. It is possible that the ADR polymorphism effects are present only in the presence of a specific, but unknown, genetic background.
5. Polymorphisms in the regions flanking the ADRβ2 and ADRα2b genes 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 ADRβ2 Gln27Glu or Glu^{12}/Glu^{9} polymorphism and a distinct and putative polymorphism at another locus within the same chromosome.

Operational Definitions

Computed tomography (CT): A technique for assessing normal 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 attention of X-rays as they pass through the body. Attenuation scores are measured in Hounsfield Units, which depend on 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.

Dual-energy x-ray absorptiometry (DXA): A technique for assessing whole and regional body composition that considers the body to be composed of three compartments: bone mineral mass, soft mass and lean tissue. Tissue amounts are based on the attenuation of x-rays as they pass through the body.

5-RM: Refers to the maximum amount of resistance an individual can move through a complete range of motion only five times

Adrenergic receptors (ADRs): a class of G-protein coupled receptors that is the target of catecholamines (Epinephrine or Norepinephrine) and activated by these, including nine subtypes: α1A, α1B, α1D; α2A, α2B, α2C; β1, β2 and β3.

ADRB2 gene: The gene encoding ADRβ2 receptor, located on chromosome 5(5q31-q32), spans ~22 kbp and contains 1 exon.

ADRA2B gene: The gene encoding ADRα2b receptor, located on chromosome 2(2p13-q13), spans ~21 kbp and contains 1 exon.

Gln27Glu polymorphism (ADRβ2 gene): Results from a C to G transition at position 79, which causes a change in the 27 residue from Glutamine to Glutamic acid at amino terminus. Genbank accession number Y00106.

Glu^{12}/Glu^{9} polymorphism (ADRα2b gene): Results from the deletion of three Glutamic acids from a Glutamic acid repeat element (Glu×12, amino acids 297-309) present in the third intracellular loop of the receptor.

Intermuscular fat (IMF): Fat interspersed within muscle, visible within the muscle area in CT images and can be distinguished with HU of -30 t0 -190

Low density muscle (LDM): Muscle with attenuation lower than 30HU but higher than 0 HU, usually due to increased fat deposit within myocytes or around muscle bundles.

Normal density muscle (NDM): Muscle with attenuation higher than 30 HU until 100 HU.

Sarcopenia: A condition characterized by the age-associated loss of muscle size and strength, accompanied by increased fat infiltration. This typically leads to or exacerbates ailments such as osteoporosis and loss of functional independence.

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 training over the past six months.

APPENDIX B: FORMS

CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

Project Title: Effects of Gene Variations on Age- and Strength Training-Induced Changes in Muscular Strength, Body Composition, Blood Pressure, Glucose Metabolism, and Lipoprotein-lipid Profiles

I state that I am over 18 years of age, in good physical health, and have elected to participate in a program of research being conducted by Dr. Ben Hurley in the Department of Kinesiology at the University of Maryland, College Park, MD 20742.

I understand that the primary purpose of this study is to assess the role that genetics may play in causing losses of muscular strength and muscle mass with age and gains in strength and muscle mass as a result of strength training. I understand that another purpose of the study will be to assess the influence of genes on changes in body composition, blood pressure, blood sugar metabolism, blood fats muscle power, and performance of common physical tasks with age and strength training.

I understand that the procedures involve three phases. During the first phase, I will undergo testing, which will include a blood draw to analyze my DNA (genetic material), blood sugar and fats, and other blood proteins. My blood pressure, body composition, bone mineral density, leg muscle volume, muscle strength, muscle power, and ability to complete selected tasks similar to common activities of daily living will also be assessed during this first phase. The second phase of the study involves my participation in a strength training program three times a week for approximately six months. The third and final phase will be a repeat of all previously taken measures, except analysis of my DNA, which will not need to be repeated. Some of the tests will be repeated both after ~ 10 weeks of training and again after the entire training program. These repeat tests will include blood pressure, strength, power, muscle volume and body composition. Other tests will be repeated only after the entire training program.

I understand that the blood draw will require providing about 2 to 3 tablespoons of blood. I understand that there is a risk of bruising, pain and, in rare cases, infection or fainting as a result of blood sampling. However, these risks to me will be minimized by allowing only qualified people to draw my blood. A portion of this blood sample will be sent to the University of Pittsburgh to analyze my DNA. I understand that the remainder will be stored at the University of Maryland for later analysis of my blood sugar, the hormone that regulates my blood sugar (insulin), blood fats, and other blood proteins. I understand that a portion of this sample may also be used for potential future studies, but only as such studies examine strength, body composition (i.e., fat, muscle & bone), metabolism of blood sugar, and blood pressure. I understand that I may contact the principal investigator at any future point in time to request that any stored blood sample be destroyed immediately.

I understand that while I am lying on a padded table, my leg muscle and fat mass will be measured by computed tomography (CT). The CT scan will be performed at Washington Adventist Hospital. My percent body fat and bone mineral density measurements will be performed at the United States Department of Agriculture in Beltsville, Maryland by dual-energy x-ray absorptiometry (DXA). This will require my lying still on a padded exam table wearing metal-free clothing for about 10 minutes at a time, totaling less than 30 total minutes for the entire procedure.

I understand that there will be a total radiation dose of no more than 1 Rem to the whole body (effective dose equivalent) from each CT scan. This amount is well below the maximal annual radiation dose (5 Rems) allowed for exposure in the workplace. The body composition and bone density testing completed by DXA involves a small radiation exposure. The radiation exposure I will receive from DXA is equal t to an exposure of less than 50 millirems to the whole body. Naturally occurring radiation (cosmic radiation, radon, etc.) produces whole body radiation of about 300 millirems per year. Therefore, the total dose of radiation exposure due to the DXA measurement is minimal and the combined dose of DXA and CT is considered low.

I understand that strength and power assessments will be performed on machines that measure how much force and how fast I can exert force through a typical range of knee extension motion. Strength testing will also be performed on the same exercise machines used for training by measuring the maximal amount of force that I can move through the full range of an exercise. During each strength training session I will be asked to exercise on machines which offer resistance against extending and flexing my arms, legs, and trunk region for approximately 40 minutes or less a day, three times a week for up to six months. I understand that I may experience some temporary muscle soreness as a result of the testing sessions. There is also a risk of muscle or skeletal injury from strength and power testing, as well as from strength training. The investigators of this study will use procedures designed to minimize this risk.

I understand that I will be asked to complete some tasks to measure my ability to carry out normal daily activities. These tasks include rising from a chair, short brisk walks and climbing a flight of stairs. Any risk of injury during the completion of these tasks will be minimized by having all sessions supervised by an exercise physiologist qualified to direct this type of testing and wearing a safety harness during the short brisk walks and climbing a flight of stairs.

I understand that it is also possible that heart or blood vessel problems could arise during my participation in the testing or training involved in this study. Although unusual, it is possible that these problems could lead to a heart attack or even death. Therefore, prior evaluation and permission from my physician at my expense will be required to participate in this study. I also understand that it is possible that these risks will not be eliminated completely, even with a medical evaluation prior to participation in the study.

I understand that this study is not designed to help me personally, but may help the investigators better understand who is likely to be most and least susceptible to losing strength, power, and muscle mass with advanced age and who is most and least likely to benefit from strength training.

I understand that my decision of whether or not to participate in this study is voluntary. I understand that I am free to ask questions about this study before I decide whether or not to participate in the study. I understand that if I consent to participate in the study I am free to withdraw from participation at any time without penalty or coercion, or without any requirement that I provide an explanation to anyone of my decision to withdraw. In addition, I understand that refusal to participate will not involve a penalty or loss of benefit to which a volunteer would ordinarily be entitled to at that time. If I am on hormone replacement therapy (HRT) prior to the study, I must remain on them and if I am not on HRT prior to the study, I must remain off them throughout the study to qualify for continued participation. If I am taking other medications prior to the study, I will be permitted to participate as long as I had been on these mediations for at

least 4 weeks prior to the study and do not stop taking them prior to the end of the study. I understand that all information collected in this study is confidential. For my participation in the study I will receive information after the study is completed about my blood pressure, blood test results, bone mineral density, body composition, and functional ability upon request, free of charge. However, I understand that I will not receive any financial compensation in exchange for my participation in this study.

In the event of physical injury resulting from participation in this study, upon my consent, emergency treatment will be available at the medical center of Washington Adventist Hospital with the understanding that any injury that requires medical attention becomes my financial responsibility. I understand that the University of Maryland at College Park will not provide any medical or hospitalization insurance coverage for participants in this research study, nor will they provide compensation for any injury sustained as a result of this research study, except as required by law.

I understand that I can discuss this research study at any time with the principal investigator, Dr. Ben Hurley at (301) 405-2457 or with the study coordinator of this project at (301) 405-2569.

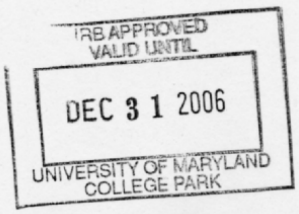
I have read and understand the above information and have been given an adequate opportunity to ask the investigators any questions I have about the study. My questions, if any, have been answered by the investigators to my satisfaction. By my signature I am indicating my decision to consent to participate voluntarily in this study.

Principal investigator: Ben Hurley, Ph.D., Dept of Kinesiology, HLHP Building, University of Maryland, College Park, MD 20742-2611, Ph: (301) 405-2486.

Printed Name of Subject_____

Signature of Subject_____ **Date**_____

Contact information of Institutional Review Board: If you have questions about your rights as a research subject or wish to report a research-related injury, please contact: Institutional Review Board Office, University of Maryland, College Park, MD 20742; e-mail, irb@deans.umd.edu; telephone, 301-405-4212.



Name of Interviewer:_____ Eligible to Participate: ___Yes ___No
Date of Interview: _____ _____Need More Information or Review

University of Maryland at College Park
Department of Kinesiology

THE GUSTO STUDY
Data Sheet for Detailed Subject Telephone Interview

AGE: _____

50 – 64 years _____
65 or older _____

o **Brief Explanation of Study**
o **Permission to Conduct Interview?** _____Yes _____No

Comment:_____

o **Contact Information**

Name: Mr. Mrs._____
Address:_____
_____
Phone #:(W)_____(H)_____
E-Mail:_____
Best Way and Time to Contact:_____

- **Time Commitment** – Available
____Yes ____No Wants to be contacted after _____(Date) Comment:_____
_____

- **Proximity to UMD Campus**
Length of commute: _____ miles or _____ minutes
Within reasonable commute_____ Willing to make unreasonable commute_____
Too far to commute_____

- **Age**
Age: _____ yrsDate of Birth: _____/_____/_____
MM DD YY
Approximate Height: _____Approximate Weight: _____

- **Racial Identification:**
___ American Indian or Alaskan Native
___ Asian or Pacific Islander
___ Black, not of Hispanic origin
___ Hispanic
___ White, not of Hispanic origin
___ Other/Unknown

- **Smoking**
Always Non-Smoker_____ Non-Smoker for _____ Smoker_____

- **Communication Log**
_____
_____
_____
_____
_____

Name: _____

- **Physical Activity**

1. Do you do any walking/jogging? _____

Hours per week? _____

Times per week?_____

Speed/Pace?_____

Hills? _____

Do you perspire? _____

2. What household jobs do you do? Gardening, housework, yardwork etc. _____

_____

_____

Hours per week? _____

Times per week?_____

Do you perspire? _____

3. Do you do any recreational activities? Sports, fishing, golfing, yoga, pilates, exercise classes etc.

_____

Hours per week? _____

Times per week?_____

Do you perspire? _____

4. What is your profession? _____

Please describe a typical day at work. _____

_____

_____

How much time each day do you spend walking around?_____

5. Do you lift any heavy objects regularly?_____

6. Is there any aspect of your physical activity that is very inconsistent or sporadic?_____

_____

Relatively Sedentary?

_____Yes _____No

Cardiovascular/Respiratory Conditions

____No ____Yes (Record on Medical History/Treatment Form)

Comments:_____

_____

- **Heart Problems**:

  Did your doctor ever tell you that you had a heart problem? ___Yes ___No

  If yes, what was the date of onset? _____

  What did the doctor call it? (Angina, Heart Failure, Heart attack, Rhythm disturbances, heart murmurs, enlarged heart, diseases of heart valves, others).

  _____

  _____

- **Osteoarthritis/Degenerative Arthritis**

  ___No ___Yes

  If yes, how long and what was the severity_____

  _____

- **High Blood Pressure**

No_____

Yes_____ Controlled (Record High BP and Treatment on Medical History/Treatment Form)

Yes_____ Uncontrolled

Comments:_____

_____

- **Lower Back Pain**

  ___No ___Yes

  If yes, how severe?_____

- **Frailty**

  No Incidents_____

  Fracture as Adult?_____ Describe:_____

  _____

  > 2 Falls in One Year?_____ Describe:_____

  _____

Comments:_____

_____

- **Diabetes**

_____No

_____Yes – Type II (Non-Insulin Dependent)

(Record Type II Diabetes and Treatment on Medical History/Treatment Form)

_____Yes – Type I – (Insulin Dependent – not qualified for the GUSTO study)

Comments:_____

_____

- **Orthopedic Conditions**

_____No

_____Yes (Record on Medical History/Treatment Form)

Comments:_____

_____

- **Stroke/Paralytic conditions**

_____Yes ____No. (If yes ask subject if there is any residual weakness of any extremity)

- **Surgical History**

___No ___Yes
If yes, what type (surgeries of the joints, heart surgeries, angioplasty, bypass surgery, Pacemakers)_____
When_____

- **Other Medical Conditions**

_____No
_____Yes (Record on Medical History/Treatment Form)
Comments:_____
_____

- **Information on where to send Physician Consent Form**

Name of Physician: _____
Specialty of Physician:_____
Have you seen your physician within the past 12 months? ____Yes ____No
Phone Number:_____
Fax Number: _____
Address (if phone and fax unknown):_____
_____
_____
(Please explain to the subject that he/she is unlikely to get med clearance if they have not seen their doc within the past 12 months and request them to go to the physician. If willing, request them to let us know after they meet their doctor and fax the med clearance form to physician AFTER they go to their doctor)

- **Summary**

Interviewer Signature: _____

Questions/ Comments:_____
_____
_____

Reviewer Initials: _____

_____Qualifies _____Need More Information
_____Needs Dr. Hurley's Review _____ Disqualified

Questions/ Comments:_____
_____

Medical Clearance to Participate in Research Project

It is my understanding that _____ (name of the volunteer), a patient under my care, has volunteered to participate in the study entitled, ***"Do Genes Influence Responses to Strength Training?"*** The volunteer must have the approval of her or his physician to participate in this study.

Exclusionary criteria for eligibility are listed below. If you believe that your patient named above has any of the medical conditions indicated below, please place a check in front of the condition(s) indicated:

____ Severe cardiovascular disease, such as ____unstable angina, ____uncontrollable hypertension, ____uncontrolled dysrhythmias, ____severe stenotic or regurgitant valvular disease, ____hypertrophic cardiomyopathy, and ____symptomatic peripheral arterial disease
____ Severe COPD or other signs of significant pulmonary dysfunction
____ Intracranial aneurysm
____ Musculoskeletal diseases that cause severe joint pain at rest or upon exertion
____ Diseases that promote muscle protein breakdown
____ Joint, vascular, abdominal or thoracic surgery in the past year
____ History of bone fragility fractures
____ Having any condition that is likely to be aggravated by muscular exertion
____ Being unable to engage safely in mild to moderate exercise, such as independently walking up at least one flight of stairs or walking two blocks on level ground

Although we are unaware of any cardiac complications that have resulted from strength testing or strength training, there is only a limited amount of data available in people over the age of 75. There is one report of non-fatal subarachnoid hemorrhage associated with strength training in three patients who had pre-existing intracranial aneurysms. For this reason, any patient who has known or suspected intracranial aneurysms or who is at high risk for having an intracranial aneurysm, should not participate in this study.

Please check one of the following:
____ Clearance granted
____ Clearance not granted
____ Please send me the following information about the study:

Volunteers in this study will participate in resistance exercise under the supervision of exercise specialists trained specifically for this study under the direction of the Principal Investigator, Ben Hurley Ph.D., Professor, Department of Kinesiology, College of Health and Human Performance, University of Maryland, College Park, Maryland 20742 (email: bh24@umail.umd.edu; tele: 301-405-2486; fax: 301-405-5578).

Physician's signature:_____ Date:_____

Name:_____ **Sex**_____ **Initials:** ___ ___

Name of Interviewer: _____ **Date:** _____

Emergency contact name, address, phone_____

_____

Have you ever been a patient at Washington Adventist Hospital? _____Yes _____No _____not sure

MEDICAL HISTORY FOR GUSTO STUDY

DIRECTIONS:

Read the following questions out loud to each prospective volunteer and check "yes" or "no". Any answers that require qualification should be written in the space below the question or on the back of the sheet.

YES NO

SECTION *A*

Musculoskeletal system:

Have you ever been told by your doctor that you have any of the following?

a. Osteoarthritis or degenerative arthritis ____ ____

b. Rheumatoid arthritis ____ ____

c. Unknown or other type of arthritis (eg: Ankylosing Spondylitis) _____ ____

d. Osteoporosis ____ ____

e. Any other disease of joint or muscle: _____ ____

Comments:_____

_____

SECTION *B*

Cardiovascular system:

1. Has any family member had a heart attack prior to the age of 55? ____ ____

   If so, please describe the relationship:

	YES	NO
2. Have you ever had frequent cramping in your legs?	____	____
If yes, is it a current problem?	____	____
3. Have you ever had pain or cramping in your legs while walking?	____	____
If yes, is it a current problem?	____	____
If yes, is this pain relieved by rest or by discontinuing your walk?	____	____
4. Have you ever been told that you have high blood pressure?	____	____

If yes,

a. What was the date of diagnosis? _____

b. Were you given any medications? ____ ____

(Please list the medications with dose on the last page)

c. How long have you been on the medications? _____ ____ ____

d. Has there been a recent change in the medications and if so, when? _____

5. Did a doctor ever tell you that you had a heart problem? ____ ____

If yes,

a. What was the date of onset?

b. What did the doctor call it? (eg: Angina, Heart Failure, Heart Attack, Rhythm disturbances, heart murmurs, enlarged heart, diseases of heart valves, others). *Please circle relevant one(s). If others, please ask subject to expl*

c. Were you given any medications? *(Please list the medications with dose on the last page)*

d. Was Echocardiography ever done? ____ ____

6. Have you ever had any chest pain or discomfort other than breast pain (in women)? or pain and discomfort due to a respiratory or digestive problem? ____ ____

If yes,

a. What was the month and year of the first occurrence? _____

b. What was the month and year of the most recent occurrence? _____

c. What was the frequency of occurrence? (eg: once a month, once a week, once a year etc.)

_____

d. How would you describe the pain or discomfort? (Eg: Pressure, Burning,

Squeezing, Piercing, Stabbing, Shooting or Sticking) *Circle appropriate one or if different, please describe*_____

How many minutes did it last?_____

e. Does the pain or discomfort move? If yes, to where?

f. Does the pain or discomfort tend to occur:

After meals-	____	____
At night-	____	____
When Exercising-	____	____
When walking in cold windy weather-	____	____
When upset, excited or nervous-	____	____
Other-		

g. Is this pain relieved by

A change in posture-	____	____
Rest-	____	____
Physical activity-	____	____
Bicarbonate of soda, Tums or antacids-	____	____
Prescribed medications-	____	____
Other-		

h. Did you ever consult a doctor for this pain or discomfort? ____ ____

If yes,

Do you know the diagnosis?_____

Were you given any medications and if so was there a recent change in the medication (within past one month)? (*Please list on last page, if yes*) _____ _____

7. Do you have any history of high cholesterol in your blood as evident by previous blood lipid tests? ____ ____

Comments:_____

_____

SECTION *C* **YES NO**

Respiratory System:

1. Have you ever had persistent cough with sputum production for almost all days for 3 months for two consecutive years? ____ ____

   If yes,

   a. How long did it last?

   b. Did your doctor prescribe any medications and has there been any recent change in the medication:

(*Please list on last page, if any*)

2. Have you ever had attacks of wheezing? ____ ____

   If yes,

   a. Was it seasonal/ periodic? ____ ____

   b. Have you ever-required hospitalization to abort an acute attack? ____ ____

Comments:_____

_____

SECTION *D*

Endocrine system:

Has your doctor ever told you that you have any of the following?

a. Thyroid problems? ____ ____

b. Adrenal problems? ____ ____

c. Diabetes mellitus? ____ ____

If yes, which type?

Date of onset-_____

Were you on any medication, diet control ____ ____

SECTION *E* **YES NO**

Reproductive system:

Menstrual History

a. Have you attained menopause? ____ ____

If so,

Are you on Hormone Replacement Therapy? ____ ____

If yes, how long have you been on hormone replacement therapy?_____

Comments:_____
_____

SECTION *F* **YES NO**

Neurological system:

1. Do you have any problems with your memory? If yes,
   a. When answering the telephone, do you recall
      what you were doing before it rang? ____ ____
   b. If someone calls you, can you give the directions to your house? ____ ____
   c. Can you keep appointments without a reminder? ____ ____
   d. Can you remember what clothes you wore yesterday? ____ ____

   If the subject answers "no" to any of the above questions

   Do a Mini Mental Status Examination of the subject.
2. Any problems with vision other than corrective lens changes? ____ ____

   If yes, which of the following conditions- Blindness, Temporary loss of vision, Double vision, Glaucoma, Cataract, Macular degeneration or others.

	YES	NO
3. Ringing in your ears?	____	____
4. Vertigo (a feeling of spinning, or unsteadiness)	____	____
5. Fainting Spells (black outs)?	____	____
6. Seizure or convulsions?	____	____
7. Migraine or severe headaches?	____	____
8. Paralysis of arm or leg?	____	____
9. A head injury with loss of consciousness?	____	____
10. Pain, numbness or tingling in your arm or hand?	____	____
11. Pain in your lower back?	_____	____
12. Kidney stones?	_____	____
13. Ruptured vertebral disc in neck or back?	_____	____
14. Have you had pain in any part of body (including headache) while exercising?	_____	____
15. Numbness or pain in your legs?	____	____
16. Have you been told that you have a peripheral neuropathy?	____	____
17. Tremors?	____	____
18. Problems with walking?	____	____
a. Do you fall frequently?	____	____
b. Is your walking problem related to pain, weakness or loss of balance?	____	____
19. Stroke?	____	____
20. Epilepsy?	____	____
21. Operations on skull or brain?	____	____
22. Multiple sclerosis?	____	____
23. Meningitis or Brain fever?	____	____
24. Parkinson's disease	____	____

25. Any history of neurological consultation? ____ ____

Comments:_____

_____

SECTION *H* **YES** **NO**

Hematology/Immunology/Oncology :

1. Have you ever been told by your physician that you had a problem with anemia or any disease of the red blood cells or the white blood cells? ____ ____
2. Any family history of this problem? ____ ____
3. Do you have any history of bleeding disorders? ____ ____
4. Have you ever been diagnosed as having cancer? ____ ____

   If yes, which organ, date of onset? _____
5. Were you given any medications, radiation or undergone any surgery? ____ ____

Comments:_____
_____

SECTION *I*

Surgical History:

Have you undergone any surgeries? (Please include abdominal surgery) _____ _____

If yes,

a. Where and for what purpose? _____
b. Date of Surgery? _____
c. Length of stay in hospital _____
d. Any complications of Surgery? _____

Comments:_____
_____

Has a doctor ever told that you have been suffering from

a) Cystic medial degeneration _____ _____

b) Any Connective tissue disorder? _____ _____

Has any of your family member had an intracranial aneurysm or bleeding? _____ _____

Have you ever been diagnosed with an abdominal aneurysm? _____ _____

History of severe pain in the abdomen? _____ _____

If yes, Please specify_____

Any history of severe headache? _____ _____

If Yes,

What was the date of onset?_____

Was it associated with neurological signs like blurred vision, nausea/vomiting, seizures, drowsiness,memory impairment,sensory or motor loss(weakness)? _____ _____

Was it a new or different type of headache other than tension, migraine etc? _____ _____

Was it the worst ever experienced? _____ _____

Did it occur after exertion, coughing or straining? _____ _____

SECTION *J*

Do you have any other health problems not covered in this questionnaire? ____ ____

If yes, please do specify.

Comments:_____
_____

Subject Name:_____ Initials: __ __ __ #: __ __ __ __ __

GUSTO

PHYSICAL ACTIVITY SCALE

(PASE)

INSTRUCTIONS:

Please complete this questionnaire by either circling the correct response or filling in the blank. Here is an example:

During the past 7 days, how often have you seen the sun?

(0) NEVER (1) SELDOM (1-2 DAYS) (2) SOMETIMES (3-4 DAYS) (3) OFTEN (5-7 DAYS)

Answer all items as accurately as possible. All information is strictly confidential.

Initials: __ __ __ #: __ __ __ __ __

LEISURE TIME ACTIVITY

1. Over the past 7 days how often did you participate in sitting activities such as reading, watching TV or doing handcrafts?

(0) NEVER ↓ GO TO Q #2 | (1) SELDOM (1-2 DAYS) ↓ | (2) SOMETIMES (3-4 DAYS) ↓ | (3) OFTEN (5-7 DAYS) ↓

1a. What were these activities?

_____

1b. On average, how many hours per day did you engage in these sitting activities?

(1) LESS THAN 1 HOUR (2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS (4) MORE THAN 4 HOURS

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for fun or exercise, walking to work, walking the dog, etc?

(0) NEVER ↓ GO TO Q #3 | (1) SELDOM (1-2 DAYS) ↓ | (2) SOMETIMES (3-4 DAYS) ↓ | (3) OFTEN (5-7 DAYS) ↓

2a. On average, how many hours per day did you spend walking?

(1) LESS THAN 1 HOUR (2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS (4) MORE THAN 4 HOURS

Initials: ___ ___ ___ #: ___ ___ ___ ___ ___

3. Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities? (Do not include walking.)

(0) NEVER	(1) SELDOM	(2) SOMETIMES	(3) OFTEN
↓	(1-2 DAYS)	(3-4 DAYS)	(5-7 DAYS)
GO TO Q #4	↓	↓	↓

3a. What were these activities?

_____

3b. On average, how many hours per day did you engage in these light sport or recreational activities?

(1) LESS THAN 1 HOUR (2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS (4) MORE THAN 4 HOURS

4. Over the past 7 days how often did you engage in moderate sport and recreational activities such as doubles tennis, ballroom dancing, hunting, ice skating, golf without a cart, softball or other similar activities? (Do not include walking.)

(0) NEVER	(1) SELDOM	(2) SOMETIMES	(3) OFTEN
↓	(1-2 DAYS)	(3-4 DAYS)	(5-7 DAYS)
GO TO Q #5	↓	↓	↓

4a. What were these activities?

_____

4b. On average, how many hours per day did you engage in these moderate sport and recreational activities?

(1) LESS THAN 1 HOUR (2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS (4) MORE THAN 4 HOURS

Initials: __ __ __ #: __ __ __ __ __

5. Over the past 7 days, how often did you engage in strenuous sport and recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross-country) or other similar activities?

(0) NEVER → GO TO Q #6

(1) SELDOM (1-2 DAYS) →

(2) SOMETIMES (3-4 DAYS) →

(3) OFTEN (5-7 DAYS) →

5a. What were these activities?

_____

5b. On average, how many hours per day did you engage in these strenuous sport and recreational activities?

(1) LESS THAN 1 HOUR

(2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS

(4) MORE THAN 4 HOURS

6. Over the past 7 days, how often did you do any exercises specifically to increase muscle strength and endurance, such as lifting weights or pushups, etc?

(0) NEVER → GO TO Q #7

(1) SELDOM (1-2 DAYS) →

(2) SOMETIMES (3-4 DAYS) →

(3) OFTEN (5-7 DAYS) →

6a. What were these activities?

_____

6b. On average, how many hours per day did you engage in exercises to increase muscle strength and endurance?

(1) LESS THAN 1 HOUR

(2) 1 BUT LESS THAN 2 HOURS

(3) 2-4 HOURS

(4) MORE THAN 4 HOURS

Initials: __ __ __ #: __ __ __ __ __

HOUSEHOLD ACTIVITY

7. During the past 7 days, have you done any light housework, such as dusting or washing dishes?

   (1) NO (2) YES

8. During the past 7 days, have you done any heavy housework or chores, such as vacuuming, scrubbing floors, washing windows, or carrying wood?

   (1) NO (2) YES

9. During the past 7 days, did you engage in any of the following activities?

Please answer YES or NO for each item.

		NO	YES
a.	Home repairs like painting, wallpapering, electrical work, etc	1	2
b.	Lawn work or yard care, including snow or leaf removal, wood chopping, etc.	1	2
c.	Outdoor gardening	1	2
d.	Caring for an other person, such as children, dependent spouse, or an other adult	1	2

Initials: __ __ __ #: __ __ __ __ __

WORK-RELATED ACTIVITY

10. During the past 7 days, did you work for pay or as a volunteer?

(1) NO (2) YES
↓

10a. How many hours per week did you work for pay and/or as a volunteer?
_____HOURS

10b. Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work?

(1) Mainly sitting with slight arm movements. (**Examples**: office worker, watchmaker, seated assembly line worker, bus driver, etc.)

(2) Sitting or standing with some walking. (**Examples**: cashier, general office worker, light tool and machinery worker.)

(3) Walking, with some handling of materials generally weighing less 50 pounds. (**Examples**: mailman, waiter/waitress, construction worker, heavy tool and machinery worker.)

(4) Walking and heavy manual work often requiring handling of materials weighing over 50 pounds. (**Examples**: lumberjack, stone mason, farm or general laborer.)

Data Entry Date: _____ Time: _____ GUSTO Team Member Initials: __ __ __
Verification Date: _____ Time: _____GUSTO Team Member Initials: __ __ __

DEXA Body Scan – USDA / University of Maryland
Conway/Hurley/Kostek

Date:_____ Time:_____am/pm

Name:_____ Gender: M / F

Date of Birth:_____

Height:_____ inches _____ cm

Weight:_____ lbs. _____ kg

Subject number:_____

Dominant leg: R / L

Time and composition of last meal (or snack):

_____
_____
_____
_____

Comments:_____
_____

Initials of examiner and DXA technician:_____

The GUSTO Study

"**G**enes **U**nderlying **S**trength **T**raining adaptations in **O**lder adults"

UNIVERSITY OF MARYLAND

College Park

To: Washington Adventist Hospital, Centralized Records & Admitting

Fax #: (301) 891-6149

From: Ben Hurley, Ph.D., Professor, Department of Kinesiology

Fax #: (301) 405-5578 Phone #: (301) 405-2569

RE: Scheduling of patients for CT muscle mass study

Patient Name _____

Previously a patient at Washington Adventist Hospital: ___Yes ___No

Date/Time for CT scan _____ DOB: _____ Age _____ Sex ___

CT scanner: ___ Old scanner ____ Newer scanner ___ Either

Address _____ Phone # _____

_____

_____

Diabetes: __Yes __No If yes, type 1 or type 2? _____ Meds: _____

Scan type: Extremity (bilateral thigh) Contrast: **NO**

Emergency Contact (relationship) _____ Phone # _____

University of Maryland / National Institute on Aging
GUSTO

Symptom-limited Baseline Knee Extension 1-RM

Arms across chest	____
Seat Belt	____
Remember to breathe	____
CHECK EACH LINE BEFORE TEST	

Examiners Name_____
Name_____ Date_____
Time _____ Location_____
Body weight_____ Age_____ Predicted 1-RM_____

Seat_____ Leg_____ Blood Pressure_____ ***Right leg / Left leg***

	Resistance	**P/D scale**	**RPE scale**
Rest	_____	_____	_____
Set 1	___0___	_____	_____
Set 2	_____	_____	_____
Set 3	_____	_____	_____
Set 4	_____	_____	_____
Set 5	_____	_____	_____
Set 6	_____	_____	_____
Set 7	_____	_____	_____
Set 8	_____	_____	_____
Set 9	_____	_____	_____
Set 10	_____	_____	_____
Set 11	_____	_____	_____
Set 12	_____	_____	_____

Most severe P/D: _____ Subject's initials: _____

Post BP_____ 3 min. post BP_____ **Valid** **Invalid**

If invalid, please explain: _____
_____
Notes: _____
_____
_____

Data entry #1:_____initials _____date	
Data entry #2:_____initials _____date	

University of Maryland / National Institute on Aging
GUSTO

Symptom-limited Post Unilateral Training Knee Extension 1-RM

Arms across chest	____
Seat Belt	____
Remember to breathe	____
CHECK EACH LINE BEFORE TEST	

Examiners Name_____
Name_____ Date_____
Time _____ Location_____
Body weight_____ Age_____ Predicted 1-RM_____

Seat_____ Leg_____ Blood Pressure_____ ***Right leg / Left leg***

Participant's initials indicating that the P/D and RPE scale is understood and that he/she has the right to stop the test at anytime _____

	Resistance	**P/D scale**	**RPE scale**
Rest	_____	_____	_____
Set 1	0	_____	_____
Set 2	_____	_____	_____
Set 3	_____	_____	_____
Set 4	_____	_____	_____
Set 5	_____	_____	_____
Set 6	_____	_____	_____
Set 7	_____	_____	_____
Set 8	_____	_____	_____
Set 9	_____	_____	_____
Set 10	_____	_____	_____
Set 11	_____	_____	_____
Set 12	_____	_____	_____

Most severe P/D: _____ Subject's initials: _____

Post BP_____ 3 min. post BP_____ **Valid** **Invalid**

If invalid, please explain: _____
_____
Notes: _____
_____
_____

Data entry #1:_____initials _____date	
Data entry #2:_____initials _____date	

DXA Result Example

HOLOGIC

```
sMay 1 18:58 2003  [327 x 150]
Hologic QDR-4500A (S/N 45816)
Whole Body Fan Beam V8.26a:3*
```

```
A11220289    Fri Nov 22 11:34 2002
Name:
Comment:     GUSTO post unilateral
I.D.:           GUSTO     Sex:     F
S.S.#:          - -       Ethnic:  W
ZIP Code:                 Height:5'10"
Operator:              M.D Weight:  133
BirthDate:                Age:     61
Physician:           GUSTO
Image not for diagnostic use
  TBAR1790 - 1
  F.S.  68.88x  @(10.88)x
  Head assumes 17.8% brain fat
  LBM 73.2% water
```

Region	Fat (grams)	Lean+BMC (grams)	% Fat (%)
L Arm	1082.4	2034.7	34.7
R Arm	1104.2	2059.6	34.9
Trunk	6946.6	21120.9	24.7
L Leg	4457.8	6865.2	39.4
R Leg	4287.2	6747.8	38.9
SubTot	17877.4	38635.4	31.5
Head	808.2	3267.2	19.8
TOTAL	18686.6	42182.6	30.7

HOLOGIC

Unilateral Strength Training

BP Questions:
1) Ever been told high Blood Pressure?
   -If yes, taken medication today and yesterday?
2) Heavy meal in past 90 minutes?
3) Had coffee/tea in past 30 minutes?
4) Smoked in past 30 minutes?
5) Any type of exercise in past 30 minutes?

Subject's Name: _____ Seat position _____ 1 RM value ____ Leg ____

Training Session #	FAM I	FAM II	1	2	3	4	5	6			
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training Session #	10	11	12	13	14	15	16	17	18	19	20
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training Session #	21	22	23	24	25	26	27	28	29	30	31
Date											
Pre-Ex .BP (mm Hg)											
5 RM*Resistance (lbs)											
Peak Ex.BP (mm Hg)											
Post Ex.BP (mm Hg)											
Weight (lbs)											

*= Weight adjusted as needed to maintain 5 RM

Training

- 5 reps @ 50% of 1 RM resistance- 30 sec rest
- 5 reps @ 5 RM resistance- 1.5 min rest
- ~5reps @ 5 RM resistance, then lower weight just enough to do 1-3 reps, repeat process until 10 total reps -2.5 min rest.
- ~5reps @ 5 RM resistance, then lower weight just enough to do 1-3 reps, repeat process until 15 total reps -3 min rest.
- ~5reps @ 5 RM resistance, then lower weight just enough to do 1-3 reps, repeat process until 20 total reps

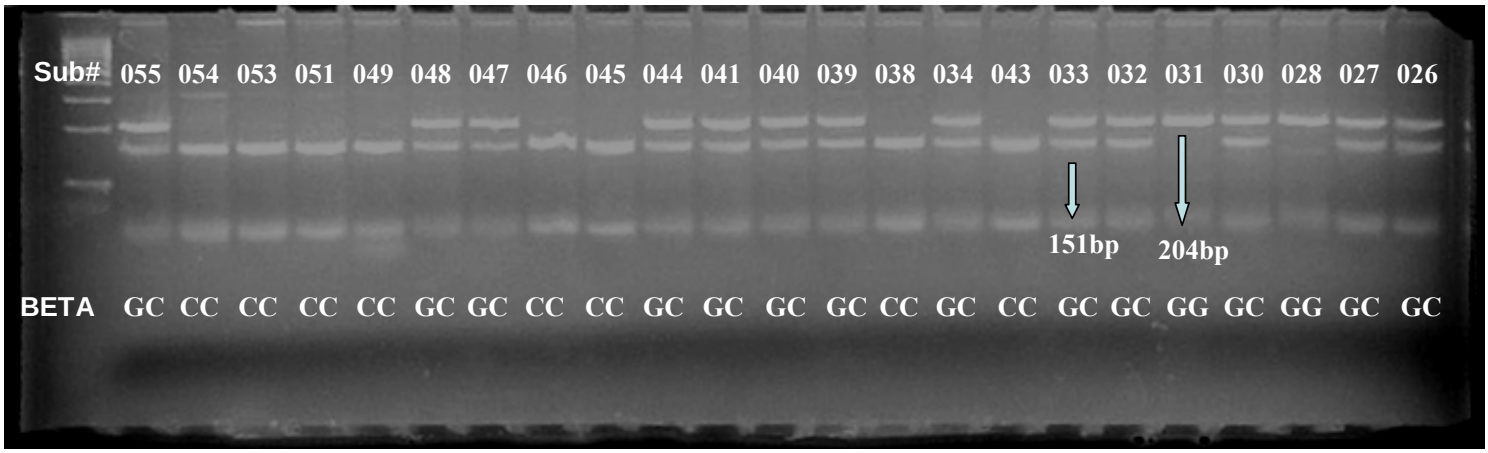
1) P/D: ___, ___, ___	2) P/D: ___, ___, ___	3) P/D: ___, ___, ___	4) P/D: ___, ___, ___	5) P/D: ___, ___, ___	6) P/D: ___, ___, ___
7) P/D: ___, ___, ___	8) P/D: ___, ___, ___	9) P/D: ___, ___, ___	10) P/D: ___, ___, ___	11) P/D: ___, ___, ___	12) P/D: ___, ___, ___
13) P/D: ___, ___, ___	14) P/D: ___, ___, ___	15) P/D: ___, ___, ___	16) P/D: ___, ___, ___	17) P/D: ___, ___, ___	18) P/D: ___, ___, ___
19) P/D: ___, ___, ___	20) P/D: ___, ___, ___	21) P/D: ___, ___, ___	22) P/D: ___, ___, ___	23) P/D: ___, ___, ___	24) P/D: ___, ___, ___
25) P/D: ___, ___, ___	26) P/D: ___, ___, ___	27) P/D: ___, ___, ___	28) P/D: ___, ___, ___	29) P/D: ___, ___, ___	30) P/D: ___, ___, ___

Comments/Notes:

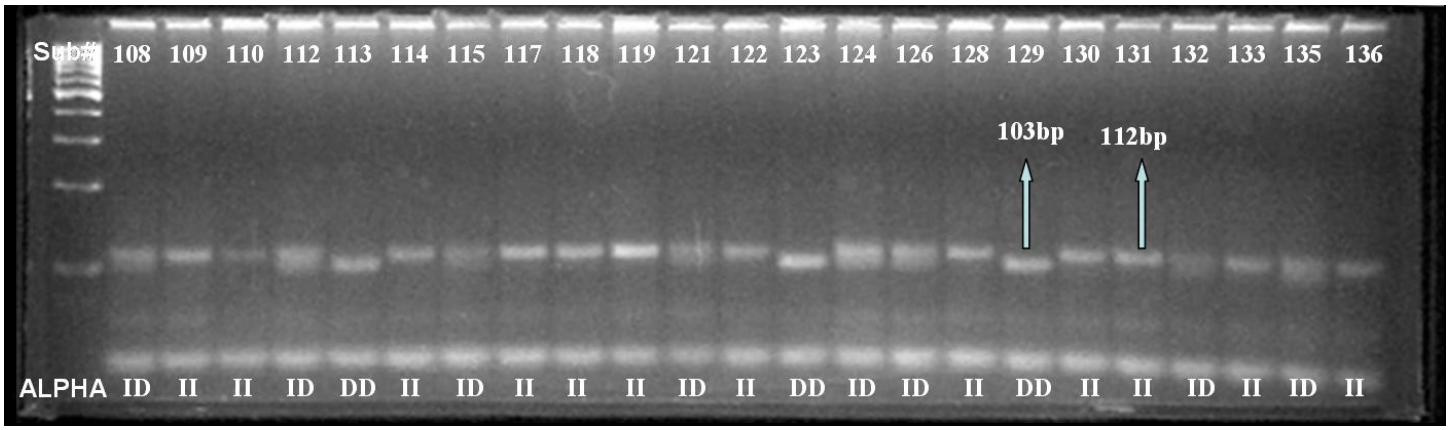
*P/D (Pain/Discomfort Scale) taken before training, after Set 2 of training, and immediately after training.

APPENDIX C: GENOTYPES

Representation of RFLP ADRβ2 Gln27Glu Genotyping Gels



Representation of RFLP ADRα2b Glu^{12}/ Glu^{9} Genotyping Gels



APPENDIX D: RAW DATA

ID Number	Age	Gender	Ethnicity	HTR	ADR beta	ADR alpha	Height	Pre total body mass	After total body mass	Pre body fat	After body fat	Pre FFM	After FFM
	yr						cm	grams	grams	grams	grams	grams	grams
HUR 011	71	M	African American	0	cc	ii	180.0	89939.9	89890.1	22434.8	22660.8	67505.0	67229.3
HUR 012	66	F	African American	0	cg	ii	168.2	70323.1	69935.2	26293.7	25922.4	44029.4	44012.8
HUR 015	78	F	Caucasian	0	cc	id	168.5	87642.3	86919.2	41978.0	40472.1	45664.3	46447.1
HUR 016	52	F	African American	1	cc	id	156.0	70965.7	69636.8	22197.1	25442.0	48768.6	47207.8
HUR 017	80	M	Caucasian	0	cc	id	160.5	66387.4	64878.0	14556.1	15087.8	51831.3	49790.2
HUR 018	77	M	Caucasian	0	cg	ii	168.6	78696.3	79607.1	22331.2	21944.7	56365.1	57662.4
HUR 021	57	F	African American	0	cc	ii	161.0	88850.9	90020.0	37774.3	36096.9	51076.6	53923.1
HUR 022	70	M	Caucasian	0	cg	id	178.9	74022.3	74738.6	17122.2	16860.8	56900.1	57877.8
HUR 023	61	F	Caucasian	0	cg	dd	165.1	62561.8	63460.4	22166.1	22483.7	40395.7	40976.7
HUR 024	53	M	African American	0	cc	id	161.5	77242.4	78799.6	23848.7	23686.5	53393.7	55113.1
HUR 025	57	F	Caucasian	1	cg	ii	169.6	90553.4	93212.9	37612.7	42014.4	52940.7	51198.5
HUR 026	59	F	African American	0	cg	ii	172.3	66658.1	66562.2	18724.1	19167.4	47934.0	47394.8
HUR 028	64	F	Caucasian	0	cg	id	160.0	63705.5	65949.4	25492.8	22774.8	38212.7	43174.6
HUR 030	57	F	Caucasian	0	cg	id	162.6	60360.4	59940.4	18755.6	17515.1	41604.8	42425.3
HUR 031	60	F	Caucasian	0	cg	id	165.0	88240.8	89788.6	39983.8	41709.8	48257.0	48078.8
HUR 032	54	M	Caucasian	0	cg	ii	168.6	95690.2	95679.2	34423.9	32962.8	61266.3	62716.4
HUR 033	62	F	Caucasian	0	gg	ii	178.0	60538.8	60788.2	17389.4	18685.6	43149.4	42102.6
HUR 034	65	F	Caucasian	1	cg	id	172.7	91013.0	88722.1	37378.5	34991.7	53634.5	53730.4
HUR 038	61	M	Caucasian	0	cc	id	164.9	63642.9	64116.6	13539.7	14039.5	50103.2	50077.1
HUR 039	77	M	Caucasian	0	cg	id	179.5	96937.1	99403.6	32204.5	32267.8	64732.6	67135.8
HUR 041	63	M	Caucasian	0	cg	ii	163.7	71623.1	70366.6	22697.8	21844.1	48925.3	48522.5
HUR 043	68	F	African American	0	cc	id	157.5	82344.6	82344.6	34103.6	33061.2	48241.0	49283.4
HUR 046	59	M	African American	0	cc	ii	161.8	82986.8	81539.0	19424.1	18106.7	63562.7	63432.3
HUR 047	54	M	Caucasian	0	cg	ii	179.6	93256.4	95524.0	29267.4	31350.0	63989.0	64174.0
HUR 048	53	F	Caucasian	0	cg	id	168.3	75573.0	75714.7	30944.7	29947.5	44628.3	45767.2
HUR 049	77	F	Caucasian	0	cc	ii	162.6	87446.3	89359.5	43610.0	43278.1	43836.3	46081.4
HUR 051	64	F	African American	0	cc	ii	165.0	67487.7	66317.6	22608.2	21988.0	44879.5	44329.6
HUR 053	67	F	Caucasian	0	cc	id	162.0	94416.3	94769.4	44338.9	41951.3	50077.4	52818.1
HUR 054	70	M	African American	0	cc	ii	184.9	89505.4	91042.5	25271.3	23917.7	64234.1	67124.8
HUR 055	61	F	Caucasian	0	cg	ii	164.7	66394.4	65610.7	26346.8	23586.0	40047.6	42024.7
HUR 056	66	F	African American	0	cc	dd	162.6	59868.2	57862.5	20578.3	18575.0	39289.9	39287.5
HUR 061	66	F	Caucasian	0	cc	ii	161.5	101073.6	105235.4	42159.3	46713.6	58914.3	58521.8
HUR 062	69	M	Caucasian	0	cg	ii	172.7	80039.3	79818.4	24209.0	22753.7	55830.3	57064.7
HUR 063	66	M	Caucasian	0	cc	id	171.2	74817.0	75012.9	23390.6	21712.3	51426.4	53300.6
HUR 064	64	M	African American	0	cc	ii	173.2	81062.4	82761.3	16257.5	15897.5	64804.9	66863.8
HUR 067	71	M	African American	0	cc	id	162.0	74556.4	75501.9	24235.8	22354.8	50320.6	53147.1
HUR 068	66	M	Caucasian	0	cg	ii	178.2	79048.4	79014.5	21256.6	20428.7	57791.8	58585.8
HUR 070	64	F	African American	0	cc	id	156.2	84814.2	86971.7	37039.3	37936.3	47774.9	49035.4
HUR 071	75	M	Caucasian	0	gg	ii	172.3	86892.8	87911.8	29124.0	28415.5	57768.8	59496.3
HUR 075	71	M	Caucasian	0	cg	id	172.1	88633.8	85652.2	25298.8	23839.7	63335.0	61812.5
HUR 076	58	F	Caucasian	0	cg	ii	160.6	61083.6	60436.7	21492.2	21873.5	39591.4	38563.2
HUR 077	70	F	Caucasian	0	cc	ii	156.4	69376.0	66214.2	26416.8	24636.4	42959.2	41577.8
HUR 078	71	M	Caucasian	0	gg	ii	168.9	75222.8	73939.8	17639.0	16042.0	57583.8	57897.8
HUR 079	71	M	Caucasian	0	cg	id	176.5	93760.5	99227.6	29124.5	34278.9	64636.0	64948.7
HUR 080	81	M	Caucasian	0	gg	id	171.0	61158.5	59955.4	13913.2	13036.0	47245.3	46919.4
HUR 081	83	F	Caucasian	1	cc	ii	143.7	57818.3	59789.1	19215.4	20499.0	38602.9	39290.1
HUR 082	68	M	African American	0	cg	ii	171.5	84053.7	84399.7	21041.6	21323.3	63012.1	63076.4
HUR 083	71	F	African American	0	cc	ii	159.5	72876.5	72285.0	31331.4	30355.0	41545.1	41930.0
HUR 084	80	F	Caucasian	0	cg	id	151.4	55558.6	54711.5	18054.7	18042.2	37503.9	36669.3
HUR 085	71	M	Caucasian	0	cc	id	190.4	114885.3	114918.4	33496.6	34465.7	81388.7	80452.7
HUR 087	62	M	Caucasian	0	cg	id	170.8	85002.5	89259.1	19482.9	22278.2	65519.6	66980.9
HUR 090	69	F	African American	0	cc	ii	160.4	78527.4	80621.3	31554.9	34199.9	46972.5	46421.4
HUR 092	65	M	Caucasian	0	cc	ii	178.7	77245.6	78766.9	17934.4	19568.4	59311.2	59198.5
HUR 093	65	F	Caucasian	1	cc	ii	162.1	78736.0	79677.4	34871.1	37318.7	43864.9	42358.7
HUR 094	65	F	Caucasian	1	cg	id	154.7	73192.6	72935.5	32213.6	33547.6	40979.0	39387.9
HUR 098	71	M	Caucasian	0	cg	dd	174.1	87644.6	87181.6	27517.3	29933.7	60127.3	57247.9
HUR 105	65	F	Caucasian	0	cc	dd	170.2	61106.1	61211.0	25519.0	23718.9	35587.1	37492.1
HUR 108	59	M	Caucasian	0	cc	id	182.2	91133.0	93822.5	35914.8	34733.2	55218.2	59089.3
HUR 110	70	F	Caucasian	0	gg	ii	154.9	67238.6	67503.4	26957.2	25587.5	40281.4	41915.9
HUR 114	70	F	Caucasian	0	cg	ii	157.5	64999.3	64520.5	24540.8	23474.9	40458.5	41045.6
HUR 115	60	M	Caucasian	0	cc	id	175.3	78666.1	77282.5	16017.9	17623.6	62648.2	59658.9
HUR 117	65	M	Caucasian	0	cc	ii	166.6	63389.2	65437.1	10991.9	11959.2	52397.3	53477.9

ID Number	Pre body fat %	After body fat %	Pre 1 RM	After 1 RM	Pre IMF	Pre LDM	Pre NDM	After IMF	After LDM	After NDM
			kg	kg	cm^2	cm^2	cm^2	cm^2	cm^2	cm^2
HUR 011	0.24	0.25	36.29	56.25	40.85	102.94	437.52	54.42	80.23	478.16
HUR 012	0.37	0.37	25.28	32.97	28.34	64.58	369.14	25.77	67.11	382.29
HUR 015	0.48	0.47	17.80	25.70	32.00	50.48	268.42	29.00	55.79	267.75
HUR 016	0.31	0.35	25.90	29.64	49.80	61.10	408.91	56.00	47.57	424.65
HUR 017	0.22	0.23	20.50	27.98	16.69	56.25	305.02	19.74	52.73	429.64
HUR 018	0.28	0.28	30.89	37.13	69.50	68.91	310.71	76.04	73.44	317.32
HUR 021	0.43	0.40	26.73	26.11	85.99	141.96	345.23	95.20	145.65	382.32
HUR 022	0.23	0.23	33.80	42.74	24.86	41.17	383.52	24.22	45.70	395.86
HUR 023	0.35	0.35	18.84	22.58	22.64	33.40	269.96	24.50	31.85	295.07
HUR 024	0.31	0.30	37.54	42.32	50.31	81.63	405.07	47.95	68.52	455.10
HUR 025	0.42	0.45	13.02	24.03	71.61	56.81	207.39	83.29	42.33	259.03
HUR 026	0.28	0.29	29.02	38.16	57.76	60.33	362.18	58.11	60.54	373.92
HUR 028	0.40	0.35	15.30	22.16	35.16	54.49	245.74	43.56	47.39	326.88
HUR 030	0.31	0.29	18.01	23.83	13.64	36.84	379.51	12.97	35.33	385.03
HUR 031	0.45	0.46	15.72	22.58	67.36	70.73	318.27	73.58	64.86	333.67
HUR 032	0.36	0.34	34.63	41.28	59.59	94.11	493.45	48.87	94.25	515.60
HUR 033	0.29	0.31	*	*	18.60	30.48	296.40	18.74	46.93	289.93
HUR 034	0.41	0.39	22.58	28.81	104.91	137.92	276.71	94.04	132.93	313.10
HUR 038	0.21	0.22	21.12	37.13	20.57	42.22	316.86	29.67	43.56	329.80
HUR 039	0.33	0.32	29.85	33.18	56.25	87.22	416.07	54.28	95.52	410.91
HUR 041	0.32	0.31	19.88	28.40	48.59	36.63	353.21	53.51	36.63	340.31
HUR 043	0.41	0.40	18.84	21.75	34.60	44.89	403.56	35.33	51.79	410.63
HUR 046	0.23	0.22	22.37	28.81	30.16	113.63	533.60	35.05	102.30	575.82
HUR 047	0.31	0.33	42.32	52.71	46.41	81.46	496.97	46.55	85.89	529.49
HUR 048	0.41	0.40	18.42	27.15	49.43	104.38	311.66	45.70	100.20	331.95
HUR 049	0.50	0.48	16.34	16.34	37.34	42.19	301.99	30.52	34.56	314.02
HUR 051	0.33	0.33	26.73	32.97	43.03	42.19	341.54	32.94	46.41	335.81
HUR 053	0.47	0.44	22.37	25.07	102.48	119.88	277.24	109.62	120.97	284.91
HUR 054	0.28	0.26	*	*	23.10	64.44	520.28	25.38	72.35	518.84
HUR 055	0.40	0.36	23.20	30.89	35.96	44.75	295.84	33.89	47.95	294.96
HUR 056	0.34	0.32	17.59	20.50	38.60	56.71	290.71	33.54	65.67	310.08
HUR 061	0.42	0.44	10.94	17.38	110.67	109.51	313.73	128.95	113.63	335.95
HUR 062	0.30	0.29	34.01	42.32	51.86	55.79	377.58	43.35	69.89	397.23
HUR 063	0.31	0.29	24.66	30.89	61.03	82.69	390.69	56.88	70.28	429.71
HUR 064	0.20	0.19	37.54	47.52	45.32	55.97	445.15	44.16	64.23	484.10
HUR 067	0.33	0.30	30.48	39.20	71.65	109.13	373.29	72.39	112.96	403.35
HUR 068	0.27	0.26	27.57	34.01	24.08	78.43	449.68	27.91	59.80	470.32
HUR 070	0.44	0.44	23.62	27.77	74.29	79.35	303.57	62.33	99.63	391.11
HUR 071	0.34	0.32	31.93	35.05	53.72	67.96	398.21	58.99	72.11	418.64
HUR 075	0.29	0.28	18.42	30.89	61.45	49.99	348.15	38.11	50.38	369.35
HUR 076	0.35	0.36	17.38	19.46	42.40	40.25	228.30	41.98	42.33	246.38
HUR 077	0.38	0.37	13.64	18.84	47.43	53.72	286.70	46.97	47.43	299.60
HUR 078	0.23	0.22	31.72	39.62	27.53	50.77	346.96	33.36	54.21	364.25
HUR 079	0.31	0.35	37.13	45.44	71.02	90.56	385.49	72.95	74.04	429.05
HUR 080	0.23	0.22	14.47	19.88	28.72	64.30	274.04	24.40	65.39	283.04
HUR 081	0.33	0.34	9.67	11.36	64.76	97.56	158.59	72.07	103.36	169.24
HUR 082	0.25	0.25	25.90	36.09	47.57	102.97	385.98	43.98	96.93	427.99
HUR 083	0.43	0.42	13.23	19.25	77.55	59.24	194.73	56.71	78.96	249.64
HUR 084	0.32	0.33	12.19	15.30	29.57	56.32	233.44	22.82	51.50	265.89
HUR 085	0.29	0.30	31.93	38.16	64.16	138.97	413.65	61.52	137.99	424.55
HUR 087	0.23	0.25	46.48	54.79	43.49	53.02	396.74	50.45	56.67	437.31
HUR 090	0.40	0.42	20.92	29.85	26.65	93.02	327.41	31.64	84.97	314.51
HUR 092	0.23	0.25	25.49	34.01	24.86	89.02	320.98	49.04	98.26	366.01
HUR 093	0.44	0.47	16.34	22.58	64.51	71.37	221.03	45.21	95.27	253.20
HUR 094	0.44	0.46	20.29	20.50	51.36	61.07	303.33	52.63	60.26	316.23
HUR 098	0.31	0.34	27.77	34.63	36.84	59.63	363.41	38.39	69.19	363.80
HUR 105	0.42	0.39	11.77	18.63	24.86	35.51	236.36	26.09	36.42	248.20
HUR 108	0.39	0.37	40.24	42.74	68.73	53.05	360.42	63.63	68.48	363.55
HUR 110	0.40	0.38	10.52	17.38	55.65	90.18	257.80	65.32	72.42	289.20
HUR 114	0.38	0.36	13.02	19.88	58.57	100.69	181.62	54.88	106.49	198.32
HUR 115	0.20	0.23	27.98	36.09	18.18	39.73	417.13	11.56	48.30	518.31
HUR 117	0.17	0.18	26.32	30.89	18.56	38.43	446.55	30.16	44.44	438.33

ID Number	Pre IMF (Untrained)	Pre LDM (Untrained)	Pre NDM (Untrained)	After IMF (Untrained)	After LDM (Untrained)	After NDM (Untrained)
	cm^2	cm^2	cm^2	cm^2	cm^2	cm^2
HUR 011	38.64	80.72	449.16	57.55	80.37	427.99
HUR 012	21.76	62.65	344.21	22.82	71.23	316.55
HUR 015	35.65	59.20	237.76	29.95	50.48	245.85
HUR 016	42.12	57.71	390.66	58.54	46.27	409.50
HUR 017	15.10	48.97	312.01	20.46	56.04	370.76
HUR 018	43.35	63.42	361.30	46.69	74.43	345.59
HUR 021	87.79	121.64	356.38	92.81	125.09	364.85
HUR 022	24.54	50.55	356.66	24.64	42.29	372.27
HUR 023	23.55	29.99	281.57	20.67	39.69	289.02
HUR 024	48.41	69.36	456.57	44.33	70.59	443.11
HUR 025	69.12	41.06	262.30	73.55	50.80	256.18
HUR 026	54.18	72.74	356.73	54.35	51.89	376.73
HUR 028	62.96	50.87	209.18	58.82	47.74	262.58
HUR 030	12.41	33.33	344.81	12.23	31.64	342.84
HUR 031	72.81	67.36	268.49	87.96	66.94	267.36
HUR 032	53.93	89.72	473.45	63.04	101.25	468.67
HUR 033	21.73	24.54	297.35	20.95	35.12	295.56
HUR 034	104.94	139.04	274.22	108.70	134.79	286.10
HUR 038	28.90	51.36	349.63	26.72	48.59	338.87
HUR 039	61.95	95.84	386.89	58.46	85.46	389.04
HUR 041	37.69	44.09	361.44	40.57	54.49	339.96
HUR 043	25.50	46.60	384.60	28.37	50.59	380.04
HUR 046	27.35	113.73	512.33	32.17	102.09	520.59
HUR 047	46.86	93.16	416.46	47.95	98.19	433.58
HUR 048	51.15	93.48	323.89	41.87	90.67	335.32
HUR 049	38.85	37.20	306.98	35.65	33.75	314.75
HUR 051	41.70	45.42	286.38	34.10	54.88	273.83
HUR 053	95.87	117.46	264.13	87.93	123.01	269.47
HUR 054	27.53	83.18	452.25	26.61	69.93	463.57
HUR 055	33.61	56.78	263.04	48.80	54.46	239.91
HUR 056	40.96	60.47	286.91	33.82	66.34	280.62
HUR 061	123.33	111.30	275.20	129.06	114.12	273.27
HUR 062	47.18	64.69	337.08	38.85	68.41	347.17
HUR 063	73.51	74.71	393.47	64.13	61.03	418.57
HUR 064	43.21	62.37	482.31	43.84	69.75	483.71
HUR 067	71.75	100.62	340.63	70.00	102.80	359.54
HUR 068	22.01	65.04	421.70	34.10	62.89	411.40
HUR 070	75.45	66.34	284.73	68.03	88.63	337.15
HUR 071	48.41	76.85	381.66	48.06	75.06	376.59
HUR 075	57.73	60.50	342.53	59.84	62.61	354.34
HUR 076	43.98	42.64	229.39	44.96	40.11	225.07
HUR 077	34.73	53.26	271.30	37.05	46.79	281.00
HUR 078	40.68	60.01	322.49	43.70	53.40	330.33
HUR 079	81.84	96.82	362.29	79.38	79.38	427.25
HUR 080	30.38	78.05	251.96	26.44	74.36	250.98
HUR 081	62.93	94.78	173.64	61.84	98.58	164.07
HUR 082	40.39	73.65	466.17	41.80	94.18	405.14
HUR 083	93.52	63.11	189.21	61.98	83.53	232.95
HUR 084	39.20	64.05	218.53	26.37	58.11	225.95
HUR 085	63.67	147.59	408.80	60.01	148.85	402.15
HUR 087	44.89	77.41	418.11	53.05	80.02	425.95
HUR 090	26.93	82.72	303.82	28.51	84.27	314.09
HUR 092	26.33	89.54	321.22	39.41	97.66	305.79
HUR 093	66.27	67.78	239.34	49.39	88.14	270.74
HUR 094	54.11	58.36	292.82	63.14	53.54	288.28
HUR 098	46.30	66.76	345.80	52.70	55.30	337.39
HUR 105	22.89	54.39	197.47	25.98	50.84	212.17
HUR 108	78.50	54.56	304.35	86.77	65.57	303.33
HUR 110	52.91	78.26	267.89	61.59	80.09	277.63
HUR 114	72.70	96.19	171.28	55.20	100.02	182.32
HUR 115	22.85	38.64	428.13	14.73	60.71	490.61
HUR 117	17.02	37.65	415.02	27.42	45.39	386.65

ID Number	Age	Gender	Ethnicity	HTR	ADR beta	ADR alpha	Height	Pre total body mass	After total body mass	Pre body fat	After body fat	Pre FFM	After FFM
	yr						cm	grams	grams	grams	grams	grams	grams
HUR 118	60	F	Caucasian	1	cg	ii	170.2	73198.1	74140.5	28979.1	28862.7	44219.0	45277.8
HUR 119	57	F	African American	0	cc	ii	162.6	75753.7	75829.9	27840.5	28359.5	47913.2	47470.4
HUR 122	56	M	Caucasian	0	cg	ii	182.9	81670.4	81744.9	25118.0	25740.4	56552.4	56004.5
HUR 123	82	F	Caucasian	0	cc	dd	158.1	58076.7	58120.0	19599.5	20411.6	38477.2	37708.4
HUR 124	66	F	Caucasian	0	cc	id	165.1	65322.4	62286.4	22039.6	19659.8	43282.8	42626.6
HUR 126	76	F	Caucasian	0	cc	id	156.2	70451.5	70470.1	31331.3	31194.3	39120.2	39275.8
HUR 128	52	F	Caucasian	0	cg	ii	157.5	50479.8	48688.3	12202.1	11840.6	38277.7	36847.7
HUR 129	52	F	Caucasian	0	cg	dd	160.0	82320.4	81812.7	33381.6	32728.1	48938.8	49084.6
HUR 130	50	F	African American	0	cc	ii	170.2	66322.4	65618.6	29165.5	28422.6	37156.9	37196.0
HUR 131	64	F	Caucasian	0	cc	ii	160.0	61819.6	61180.7	21228.3	21206.9	40591.3	39973.8
HUR 133	51	F	African American	0	cc	ii	162.6	81350.2	81178.4	31397.1	30941.9	49953.1	50236.5
HUR 135	64	M	Caucasian	0	cc	id	177.8	76631.7	76997.9	24239.6	23103.0	52392.1	53894.9
HUR 137	50	F	African American	0	cc	ii	167.6	81640.1	82065.0	33602.3	32593.9	48037.8	49471.1
HUR 138	64	F	African American	0	cg	ii	170.2	69346.5	69109.9	24573.2	25668.4	44773.3	43441.5
HUR 139	51	M	Caucasian	0	cg	ii	180.3	91414.5	91209.2	19582.0	19821.8	71832.5	71387.4
HUR 145	56	M	African American	0	cc	ii	170.2	99695.5	100243.6	29551.8	27760.9	70143.7	72482.7
HUR 149	56	F	African American	0	cg	id	162.6	69100.3	68969.1	24411.0	23112.4	44689.3	45856.7
HUR 150	56	M	African American	0	cc	id	167.6	88588.3	89533.4	20495.2	19377.4	68093.1	70156.0
HUR 151	50	F	Caucasian	0	cg	id	162.6	61646.4	61484.1	23061.6	22845.9	38584.8	38638.2
HUR 156	61	M	Caucasian	0	cc	id	177.8	111031.2	111542.7	37702.1	37730.3	73329.1	73812.4
HUR 160	61	M	African American	0	cc	ii	172.7	76462.6	74951.5	20240.5	19362.7	56222.1	55588.8
HUR 161	58	M	Caucasian	0	cg	ii	175.3	88323.6	87626.8	25943.1	25359.7	62380.5	62267.1
HUR 164	52	M	African American	0	cc	ii	178.9	66682.4	68452.8	14861.5	14193.0	51820.9	54259.8
HUR 168	67	M	Caucasian	0	cg	ii	168.8	79433.6	80114.5	20586.8	21438.1	58846.8	58676.4
HUR 169	64	F	Caucasian	0	cg	id	157.5	56524.1	54453.2	20871.7	20471.5	35652.4	33981.7
HUR 171	74	M	African American	0	cc	id	182.8	78924.9	80346.9	14866.2	16831.2	64058.7	63515.7
HUR 172	56	M	Caucasian	0	gg	id	172.7	82605.9	81950.9	21650.5	21299.3	60955.4	60651.6
HUR 174	74	M	Caucasian	0	gg	ii	183.7	84638.3	84692.6	19046.4	18523.4	65591.9	66169.2
HUR 175	51	M	Caucasian	0	cc	id	167.9	101836.7	102728.8	36392.2	34770.8	65444.5	67958.0
HUR 182	59	M	Caucasian	0	cc	id	179.0	81699.2	82249.6	23356.6	22145.4	58342.6	60104.2
HUR 183	57	F	Caucasian	0	cc	id	162.1	82699.0	82520.8	34377.9	33100.7	48321.1	49420.1
HUR 184	52	F	African American	0	cc	ii	166.1	86061.7	87867.9	33847.9	33970.8	52213.8	53897.1
HUR 187	58	F	Caucasian	0	cc	id	158.3	98148.5	96916.1	44629.9	41872.1	53518.6	55044.0
HUR 188	50	M	Caucasian	0	cg	id	177.1	119200.5	119349.0	40341.1	40167.6	78859.4	79181.4
HUR 190	53	F	African American	0	cg	ii	164.3	75741.8	76574.4	31398.7	30773.9	44343.1	45800.5
HUR 192	54	F	African American	0	cc	ii	165.5	81143.0	82375.0	37254.6	38053.1	43888.4	44322.4

ID Number	Pre body fat %	After body fat %	Pre 1 RM	After 1 RM	Pre IMF	Pre LDM	Pre NDM	After IMF	After LDM	After NDM
			kg	kg	cm^2	cm^2	cm^2	cm^2	cm^2	cm^2
HUR 118	0.40	0.39	12.19	22.58	27.32	62.93	311.17	26.23	61.45	324.46
HUR 119	0.37	0.37	35.46	38.16	49.75	72.60	332.61	49.29	54.77	357.61
HUR 122	0.31	0.31	32.97	42.32	31.46	77.06	348.54	31.43	64.34	383.77
HUR 123	0.34	0.35	13.23	20.08	40.61	37.58	211.57	36.81	71.05	259.77
HUR 124	0.34	0.32	22.58	25.07	29.32	42.54	327.90	22.08	31.75	344.46
HUR 126	0.44	0.44	11.15	13.23	63.74	56.88	207.39	44.82	86.91	237.52
HUR 128	0.24	0.24	17.38	18.84	19.34	35.02	334.65	24.89	39.09	339.86
HUR 129	0.41	0.40	20.08	28.40	41.10	61.59	339.57	31.78	89.26	381.69
HUR 130	0.44	0.43	12.60	19.46	48.97	39.27	182.21	51.93	38.46	169.73
HUR 131	0.34	0.35	11.15	16.34	22.61	40.71	237.62	26.68	40.46	261.53
HUR 133	0.39	0.38	28.40	34.22	62.68	81.91	306.18	55.51	79.59	323.54
HUR 135	0.32	0.30	29.85	38.37	19.79	34.52	359.89	28.48	35.09	262.93
HUR 137	0.41	0.40	20.08	26.73	84.38	56.60	326.04	61.10	41.45	356.91
HUR 138	0.35	0.37	20.50	20.92	50.66	46.05	292.43	45.14	48.27	297.28
HUR 139	0.21	0.22	45.85	53.75	39.48	70.00	556.70	34.35	79.59	549.42
HUR 145	0.30	0.28	39.83	65.18	116.16	171.56	533.92	107.68	170.58	547.07
HUR 149	0.35	0.34	18.00	18.42	51.12	41.94	299.39	51.71	51.93	311.63
HUR 150	0.23	0.22	38.16	60.19	47.64	75.30	492.33	54.21	65.29	565.63
HUR 151	0.37	0.37	17.38	20.50	34.49	45.39	218.64	26.09	41.48	278.05
HUR 156	0.34	0.34	44.61	64.14	68.20	118.58	482.13	58.01	119.64	518.87
HUR 160	0.26	0.26	26.73	37.96	35.82	74.74	421.95	32.17	52.77	437.34
HUR 161	0.29	0.29	37.13	45.44	37.51	71.96	410.63	40.08	94.43	385.03
HUR 164	0.22	0.21	28.81	37.13	44.40	49.08	376.91	30.73	44.44	430.49
HUR 168	0.26	0.27	29.64	32.97	45.63	84.66	338.77	56.14	85.78	354.23
HUR 169	0.37	0.38	10.73	15.30	19.27	54.00	243.74	18.07	43.56	258.61
HUR 171	0.19	0.21	34.01	40.24	24.01	81.35	418.01	37.72	56.25	471.23
HUR 172	0.26	0.26	35.05	42.32	36.14	67.22	480.97	37.13	44.61	499.61
HUR 174	0.23	0.22	35.05	46.48	37.27	82.51	372.30	32.24	61.66	424.86
HUR 175	0.36	0.34	30.89	40.24	67.11	112.82	474.61	53.44	114.29	482.94
HUR 182	0.29	0.27	47.52	57.91	37.16	77.91	412.28	41.20	70.63	451.65
HUR 183	0.42	0.40	*	*	52.73	69.26	299.57	43.80	68.70	355.04
HUR 184	0.39	0.39	34.01	40.66	113.20	96.75	385.70	113.24	88.88	355.89
HUR 187	0.45	0.43	20.92	24.66	81.28	81.77	311.27	80.79	108.04	394.14
HUR 188	0.34	0.34	50.63	64.14	78.15	120.16	401.59	79.21	109.93	474.36
HUR 190	0.41	0.40	21.95	31.93	52.66	62.19	295.52	35.37	63.74	395.61
HUR 192	0.46	0.46	23.62	30.48	61.80	59.45	285.01	63.25	64.41	290.25

ID Number	Pre IMF (Untrained)	Pre LDM (Untrained)	Pre NDM (Untrained)	After IMF (Untrained)	After LDM (Untrained)	After NDM (Untrained)
	cm^2	cm^2	cm^2	cm^2	cm^2	cm^2
HUR 118	31.50	59.45	300.83	33.29	54.49	308.21
HUR 119	55.90	53.86	333.49	52.45	59.66	316.05
HUR 122	34.24	57.76	341.16	35.65	72.25	322.66
HUR 123	45.21	44.58	194.34	38.43	52.77	259.28
HUR 124	30.16	44.19	322.42	22.61	33.15	320.24
HUR 126	65.53	41.06	262.30	38.78	70.03	258.86
HUR 128	23.73	34.52	297.60	24.71	35.86	287.33
HUR 129	47.29	58.39	288.11	45.04	93.38	361.83
HUR 130	80.61	44.72	147.76	74.85	38.99	134.65
HUR 131	27.35	31.75	243.77	31.18	38.74	243.63
HUR 133	66.13	88.73	287.75	61.95	91.51	295.95
HUR 135	18.14	37.20	407.71	32.77	37.27	276.29
HUR 137	74.85	50.70	358.70	50.63	57.76	351.53
HUR 138	37.97	36.07	314.09	46.55	37.05	297.28
HUR 139	38.81	92.21	522.14	34.14	69.89	551.53
HUR 145	75.90	169.17	469.62	61.31	151.24	520.73
HUR 149	66.27	47.95	283.25	72.32	43.45	288.35
HUR 150	48.02	96.86	458.12	56.14	82.97	497.14
HUR 151	38.29	35.12	217.86	27.42	40.54	260.26
HUR 156	53.89	127.23	424.86	54.91	134.65	421.00
HUR 160	30.20	56.11	433.76	27.91	52.45	411.29
HUR 161	35.05	84.66	387.25	39.83	67.11	405.67
HUR 164	42.47	43.70	337.78	36.25	48.27	367.95
HUR 168	44.09	70.73	353.18	44.37	69.43	363.76
HUR 169	20.92	50.17	236.74	22.68	48.13	242.47
HUR 171	24.54	62.23	425.25	41.20	71.61	418.54
HUR 172	40.01	50.94	458.09	43.38	37.90	451.58
HUR 174	42.12	76.43	394.00	38.04	74.32	414.42
HUR 175	69.86	107.09	461.64	51.61	105.05	451.76
HUR 182	36.60	61.63	428.77	40.64	58.39	437.13
HUR 183	54.49	49.64	325.02	45.53	64.90	328.22
HUR 184	92.71	86.59	375.29	97.66	62.75	325.65
HUR 187	80.61	70.45	266.41	73.23	84.41	333.63
HUR 188	82.79	103.78	455.20	77.06	119.71	389.39
HUR 190	47.00	51.47	286.88	39.97	59.70	349.52
HUR 192	76.04	67.71	239.17	64.93	69.01	243.67

APPENDIX E: LITERATURE REVIEW

The following review of literature provides background information on sarcopenia and includes a review on fat infiltration, strength training (ST) as an intervention for sarcopenia, and the role of genetics in influencing ST adaptations. This review will focus on the following topics: 1) Sarcopenia: muscle loss and fat infiltration, 2) Interventions for sarcopenia 3) Genetics of ST adaptation, and 4) Influences of ADR polymorphisms on lipid metabolism

Sarcopenia: muscle loss and fat infiltration

Sarcopenia is defined as the loss of muscle mass with aging, which subsequently affects muscle strength, power, and functional abilities (1, 35). These losses are associated with multiple adverse health outcomes in the elderly, such as frailty, increased risks of falls and fracture, osteoporosis, glucose intolerance and eventually, the loss of independence (36-38). Because sarcopenia is considered a multifactorial condition that to some extent occurs as a natural part of aging, no single factor has been identified that explains entirely the aging-related loss of muscle size or function. However, there is significant inter-individual variability in sarcopenia. Some of the major factors that appear to contribute to sarcopenia are decreases in motor neurons, anabolic hormones (sex steroids and growth hormone), protein consumption, and a rise in catabolic stimuli, such as cortisol and cytokines (e.g. interleukin-6, 1 and tumor necrosis factor - α) (39, 40).

Baumgartner et al. (41) defined sarcopenia as stature-adjusted appendicular skeletal muscle (SM) mass (i.e., SM mass / height ^{2}) more than 2 standard deviations

(SD) below the mean of a young reference population. With this definition, among 808 subjects up to 30% of women and 50% of men over age 80 years were classified as sarcopenic in the New Mexico Elder Health Survey (41). Janssen et al. (42) studied the older men (n = 2224) and women (n = 2278) from the Third National Health and Nutrition Examination Survey with SM mass percent of body weight for defining sarcopenia as class I (-1 SD to -2 SD) and class II (> -2SD). The prevalence of class I sarcopenia is 59% and 45% in older women and in older men, respectively, and the prevalence of class II sarcopenia is 10% for older women and 9% for older men. Moreover, the recent data quantifying appendicular skeletal muscle mass in ~ 200 women aged 64 – 93 and ~ 140 men aged 64 – 92 yr, found that the overall prevalence of sarcopenia was ~ 23% in women and ~ 27% in men and up to 45% in those over the age of 80 (43). These results indicate that sarcopenia affects a large number of elderly populations.

Numerous studies have shown that SM mass or size is smaller in older people in comparison to younger people as measured by various methods (44-54). The cross-sectional data from Janssen et al. (48) demonstrated that muscle mass remains relatively constant until the 40s, and then starts to decline after 45 yrs. Estimations based on the longitudinal studies (55-57) showed that SM mass decreases at a rate of 6% per year and that ~ one quarter of SM mass is lost by 85 years of age. Muscle loss is mostly observed as decreased cross-sectional area (CSA) and decreased number of muscle fibers, especially type 2 fibers. Young et al. (47) found that quadriceps CSA was 23% and 33% smaller in elderly men and women, respectively, than in younger subjects. These data are supported by the later work of Hakkinen

(58) who found a 27% lower mid-thigh CSA in older women when compared to younger women. Moreover, the loss of muscle mass was greater in the lower extremities. The initial amount of muscle mass and the rate of muscle loss with aging determine the progression of sarcopenia (59). There are few studies examining the effect of gender and ethnicity on sarcopenia. Several cross-sectional studies found that there was more age-associated SM loss in men than in women (48, 53, 60). In regard to the effect of race, one study found greater age-associated losses in SM among African–Americans than Caucasians (53), whereas another study supported the opposite finding (61).

Age –associated loss of muscle strength and power is one important component of sarcopenia. Muscle volume and strength reach a peak between 40 and 50 yrs of age and remain relatively stable until the 60s. Beginning at ~ age 60, muscle strength will begin to decline at approximately 12 – 14% per decade (54). This is equivalent to a loss of muscle function of ~ 40% by the 80s and often leads to disability and morbidity and is even associated with increased mortality (62, 63). Loss of muscle mass plays an important role in the reduction of muscle strength, while other factors such as SM composition (5), and contractile protein level also contributes to the declining muscle strength with aging (52). The loss of muscle mass and strength will affect functional abilities, possibly leading to functional impairments and disabilities with aging. Baumgartner et al. (41) reported that sarcopenic men and women have a 3 to 4 times higher odds ratio of disability than older people with normal muscle mass. Janssen et al. (42) reported a two to three-fold greater likelihood of disabilities in older men and women with sarcopenia compared to those without sarcopenia. Both

studies adjusted for age, race, obesity, health behaviors and comorbidity. Thus, sarcopenia is strongly associated with functional limitations and disabilities in the elderly. Furthermore, it has been reported that adjusted arm muscle area is a better predictor of mortality than body mass index (BMI), which is often used as a predictor of mortality in older adults (63).

Recently, the components of sarcopenia have been extended to include increased fat infiltration into skeletal muscle corresponding to muscle mass and strength loss. Significant changes in body composition with aging, such as increased body fat and decreased muscle mass have been observed in several studies (53, 64, 65). For example, it was estimated that adults aged 30 to 60 yrs gained ~ one pound of body fat and lost half a pound of muscle mass on average every year. That would be equivalent to a gain of 30 pounds of fat and a loss of 15 pounds of muscle. This increase in fat mass often masked a concomitant decrease in SM, because of a relative constancy in body weight in the elderly. The cross-sectional data (66) demonstrated that healthy men 25 yrs of age have ~ 20% body fat, while men 55 yrs of age have ~ 30 % body fat. The hypothesis that aging is associated with increases in fat and connective tissues is supported by several studies (67, 68). More recent longitudinal (2) and cross sectional studies (69) showed that not only is total body fat increases associated with aging, but regional fat infiltration into muscle increases with age, or at least associated with aging.

Fat infiltrates into SM through either depositing extra amounts of triglyceride (TG) near the mitochondria within myocytes, i.e intramyocellular TG (imTG) or around muscle fibers or bundles, i.e extramyocellular TG. Magnetic resonance spectroscopy

(MRS) is the only non invasive method that can distinguish imTG from extramyocellular TG, but it is expensive and time consuming. Other methods used to measure SM lipid content include muscle biopsy and computer tomography (CT). Biopsies have several limitations, such as being an invasive technique and poor reliability (70). CT measured tissue composition is based on the intensity value (Hounsfield Unit, HU), with advantages such as being noninvasive, inexpensive, and high accuracy. Kelley et al. (19) found muscle attenuation in CT was lower in obese subjects than in lean subjects, due to the high content of imTG and extramyocellular TG. The low density muscle (LDM) was defined by Goodpaster et al. (71) as muscle with attenuation of 0 to ~ 30 (Housfield Unit, HU), comparing to normal density muscle (NDM) having an attenuation of ~ 30 to ~ 100 HU. Increasing amount of fat interspersed between muscle groups, i.e. intermuscular fat (IMF) is another form of fat infiltration. IMF can be easily distinguished from SM and LDM due to a much smaller density of -190 to -30 HU in CT imaging.

A number of studies (2, 46, 68, 69, 72) have shown that LDM and IMF increase with aging. Song et al. (2) followed 26 African American (AA) women for two years and observed increases in visceral fat and IMF corresponding with reductions in SM. Ryan et al. (69) investigated 72 women with wide range of body fat in a cross-sectional study and found that mid-thigh LDM significantly correlates with age.

LDM and thigh IMF may be linked to age-related insulin resistance in muscle. Insulin resistance is a main risk factor for type 2 diabetes and cardiovascular diseases, which are common in the elderly. Goodpaster et al. (73) examined 54 healthy sedentary men and women and found that muscle attenuation contributed to insulin

sensitivity, independent of visceral and subcutaneous abdominal fat. In obese subjects, muscle attenuation is the strongest single correlate of insulin resistance. Moreover, Cuff et al. (10) reported that a reduction in LDM induced by ST and aerobic training (AT) combined, independently resulted in an improved glucose disposal rate. Goodpaster et al. (4) compared mid-thigh IMF, subcutaneous fat and muscle attenuation among obese subjects with type 2 diabetes, obese and lean subjects. IMF was highest in obese subjects with diabetes and a strong predictor of insulin resistance, although it only accounted for 3% of thigh fat mass. Subcutaneous adipose tissue, however, did not correlate with insulin resistance. Goodpaster et al. (3) then further identified this association in 2,964 elderly men and women (aged 73.6 yrs) by showing that both elderly men and women accumulated an increasing amount of IMF from the status of normal glucose, glucose impaired to the status of type 2 Diabetes. Moreover, the higher amount of IMF and abdominal VAT was associated with higher fasting insulin in normal weight men and women. However, Janssen et al. (11) did not observe any metabolic improvements resulting from the reduction of IMF by energy restrictive diet combined with either ST or AT.

In addition to metabolic disorders, LDM was recently reported to be associated with loss of muscle strength (5), and with the decline in leg function and with mobility limitation in the elderly (6). Goodpaster et al. (5) examined nearly 3000 older subjects from the Health ABC study and found that mid-thigh muscle attenuation was lowest in the eldest men and women; lower muscle density was associated with lower specific force production ($r=0.26$, $P<0.01$), which was independent from mid-thigh muscle mass and adipose tissue. Visser et al. (6) studied

subjects with similar characteristics of those in the Health ABC study and found that the reduced muscle attenuation was associated with a poorer lower leg performance (measured by a 6-meter walk and repeated chair stands), independent of total body fat and muscle area. Then, Visser et al. (7) followed up these subjects for 2.5 years. Mobility limitations were developed in 22.3% of the men and in 31.8% of the women. The hazard ratio of developing mobility limitations in subjects who had the lowest muscle attenuation was 2.16 times higher than those who had the highest muscle attenuation. These findings indicate that muscle attenuation (the reflection of muscle lipid content), together with muscle strength and muscle mass, is a predictor of incident mobility limitations in well-functioning older persons.

The mechanisms under which fat infiltration increases with aging are not known. TG is formed by esterifying free fatty acids to glycerol (lipogenesis). To use fat as a fuel, TG must first be hydrolyzed (lipolysis) and the resultant fatty acids are then transported by blood flow to skeletal muscle mitochondria for oxidation. The regulation of adipose tissue lipolytic activity is involved in the release of catecholamines (norepinephrine and epinephrine), binding to adrenergic receptors (ADRs) and activating hormone-sensitive lipase. At rest, the amount of fatty acids released from adipose tissue typically exceeds the amount oxidized, while mid or moderate–intensity exercise is associated with a 5-10 fold increase in fat oxidation above resting amounts. Some studies (74, 75) found a decreased lipid oxidation rate within SM in a resting stage in the older people. Therefore, it is possible that changes in SM occur as a natural aging process. Other factors possibly contribute to the increased fat infiltration into SM with aging. For example, high saturated fat intake in

the older individuals and leptin resistance possibly increase lipogenesis (76). Moreover, a decreased level of social and physical activity with advancing age may lead to decreased lipolysis and oxidation in the elderly.

Genetic determinants may also influence fat infiltration in the aging muscle. The ADR genes are of particular importance for the fat deposition and distribution because of the central role of catecholamines in the regulation of lipolysis and energy expenditure. For example, Large et al. (77) found that G allele carriers of ADRβ2 C-27G polymorphism tend to possess more fat than noncarriers. ADRα2b Glu^9/Glu^9 carriers have decreased basal metabolic rates (78). For this reason, those who have specific genetic backgrounds may be prone to the accumulation of more fat in skeletal muscle with aging. The influence of ADR gene polymorphisms on lipid metabolism will be discussed in detail in the latter part of this review.

Interventions for Sarcopenia

As a result of the increased prevalence of sarcopenia, the total health care costs and detrimental physical consequences that follow, it is imperative from a public health perspective to find a safe and effective method to increase muscle strength and mass in the elderly. Hormonal interventions, nutritional supplements and strength training have been investigated to determine their effectiveness for slowing or reversing sarcopenia.

Hormonal Interventions. Based on evidence that age-related decline in growth hormone (GH) and insulin-like growth hormone-1 (IGF-1) may contribute to the development of sarcopenia (79-81), several studies (82-85) have addressed the question of whether age–associated muscle loss can be reversed through GH

supplements. Rudman et al. (82) observed a 8.8% increase in lean body mass resulting from 6 months of subcutaneous GH injections in 21 healthy men aged 61 to 81 yrs. The effect of GH supplements on muscle strength was not tested in this study. When the trial period was elongated to 12 month in another study (83) conducted by the same group, a resulting 6% increase in lean body mass was accompanied by substantial frequency of adverse side effects such as carpal tunnel syndrome, gynaecomastia and hyperglycaemia. All participants in these two studies had low serum IGF-1 levels before supplementation, but these levels were restored within the normal range after GH supplementation. Moreover, Papadakis et al. (84) tested the knee and handgrip strength after GH administration, but did not see any differences between supplement group and control group, although the lean body mass was increased with GH administration. The incidence of side effects in the GH group was consistently higher than in the control group. Chu et al. (85) reported that 4 weeks of low dose GH administration plus dietary interventions increased lean body mass, which was subsequently associated with a faster walking speed. In all of these studies, incidence of adverse effects in the GH group was significantly higher than in the placebo group. Moreover, the administration of GH in critically ill older subjects may result in increased mortality (86). Thus, clinical utility of GH supplement is limited because of little effect on muscle strength and high incidence of adverse effects, as well as the high cost. The other two alternate strategies of enhancing GH/IGF-1 pathway are administration of growth hormone releasing hormone (GHRH) (87, 88) and the complex of IGF-1 with its major circulating binding protein (89). More investigation is needed to determine their effectiveness (90).

Cross-sectional (91-93) and longitudinal studies (94, 95) have shown that testosterone level declines with age. In a Boston area aging study, at least 4% of those between 40 and 70 years of age had severe androgen deficiency, without any symptoms (92). Data from the Baltimore Longitudinal Study of Aging (BLSA) (96), demonstrated that testosterone level is not only lower in the elderly, but also begins to decline progressively with aging, starting in the 30s. Lower testosterone concentration has been linked to decreased FFM and reduced muscle strength in both animals (97) and human (98). Based on the rational that anabolic testosterone may increase on muscle mass, therefore leading to improved functional abilities, a number of studies have tested the effect of intramuscular administration of testosterone on age-associated loss of muscle mass and strength (99, 100). The physiological dose of testosterone administation in elderly hypogonadal men resulted in increases in muscle mass (101-105), strength (99, 104, 106, 107), functional abilities (99), and a decrease in body fat (103-105, 108). In contrast, the physiological dose supplement of testosterone has no effect on muscle strength in eugonadal individuals, although muscle mass is increased. The supraphysiologic dose of testosterone, however, induced increases in muscle mass and muscle strength in elderly eugonadal men (109, 110). The adverse effects of testosterone administration can be relatively severe. For example, Tenover et al. (101) reported elevated level of prostate specific antigen and hematocrit levels. Other potential adverse effects include prostate carcinoma and provocation of aggressive behaviors.

Some studies tested the effect of dehydroepiandrosterone (DHEA), which is the precursor of adrenal sex steroids on muscle mass and strength. However, the results

are controversial since some studies found significant increases in muscle mass and strength in men, but not in women (111), whereas, other studies did not observe any effects on muscle mass or strength in men or women (112, 113). Thus, further studies are needed before any definitive conclusions can be reached on the efficacy of DHEA as an intervention for sarcopenia.

Body composition was found to change with normal menopausal transition. For example, Poehlman et al.(114) observed a 3 kg loss of lean body mass, but 2.5 kg accumulation of fat mass in 35 women experienced menopause over years, compared to age-matched group who remained premenopausal This provides a rational for estrogen replacement to reverse muscle mass loss in elderly women. However, the information on this effect is limited and the available results fail to support an effect of estrogen supplement on sarcopenia. For example, Baumgartner et al. (115) compared a group of elderly women who received estrogen supplements with a control group of similar age, and found that estrogen supplement therapy is not associated with either increases in muscle mass or strength. Although these results were supported by other studies (116, 117), the data from Sorensen et al. (118) showed an association between estrogen supplement therapy and a significant increase in lean body mass and decrease in total fat mass. In conclusion, the effects of hormonal (GH, testosterone and estrogen) interventions on sarcopenia are not optimal and have adverse effects on the health status of the elderly.

Nutritional Supplements. The loss of muscle mass must be a result of net muscle protein breakdown; i. e. muscle protein breakdown exceeds muscle synthesis over a particular period of time. Thus, inadequate protein intake and unbalanced protein

metabolism may contribute to the development of sarcopenia. Food and energy intake appeared to be reduced in older adults (119). Numerous data have indicated that inadequate protein intake is associated with muscle atrophy in the elderly (120). All of this suggests that modifications in nutritional habits, especially protein and amino acid intake, may help to counteract the age-associated loss of muscle mass.

Whether protein intake requirement is modified during aging remains questionable. Some studies support recommending higher protein intakes with advanced age due to age-related losses of muscle mass, functional abilities and declines in protein intake (121, 122), whereas other studies (120, 123) found minimal change with age in protein needs and utilization. For example, Campbell et al. (122) placed 10 healthy older men and women on eucaloric diet with Recommended Dietary Allowance (RDA) protein (0.8 g / kg / day) for 14 weeks. The mid-thigh cross sectional area significantly decreased and the protein excretion declined, suggesting adaptation to low protein intake. These data suggest that the protein RDA for the elderly may be set too low to preserve muscle mass in these older people. However, more studies are needed to define new RDA for the elderly because of the mixed results from previous studies. Although the available information is insufficient to make a firm recommendation on an increase in protein intake of older people, it is clear that it is important to maintain adequate protein intake in the elderly to counter the initial development of sarcopenia. Castaneda et al (124, 125) clearly demonstrated that low protein diet (56% RDA) for 10 weeks resulted in significant loss of muscle mass and functions in elderly women, while elderly women who consumed 115% RDA protein successfully maintained the muscle mass and strength.

Essential amino acids, particularly branched amino acids like leucine, can induce stimuli in muscle protein synthesis while nonessential amino acids fail to induce even at a very high dose in both young and older people (126-128). Pannemans et al. (129) reported that protein deriving from vegetables which contains incomplete essential amino acids caused less net protein synthesis than protein deriving from animals in the elderly women. The stimulation of protein synthesis by leucine-rich meal was seen in old rats (130, 131), and this effect lasted at least 10 days, suggesting that a long-term utilization of leucine may prevent the muscle wasting with age. Clarkson et al. (132, 133) studied the effect of creatine on muscle mass, muscle strength and muscle performance. A 30 day oral creatine supplement results in only small increases in muscle performance in the men over the age of 60 years. There are no significant differences in fat free mass and muscle strength between creatine supplement and creatine non-supplement group.

The protein digestion rate influences protein retention. For example, Boirie et al. (134) found that proteins with a fast absorption rate resulted in high plasma amino acid levels, which was associated with an increased whole-body protein synthesis and oxidation, and no change in protein breakdown; whereas, the protein with slow absorption rate slightly increased protein synthesis and oxidation. When the discrepancy in amino acids composition is considered, proteins with good absorption rate still have better postprandial utilities. Therefore, a quick and easily digested protein mixture may help increase protein retention in the elderly. In addition, Volpi et al. (135) showed that the different way of amino acids are administered (intravenous or oral) did not result in different plasma amino acids level.

Despite these findings, no apparent beneficial effect has been observed in prior attempts to counter sarcopenia (36, 136, 137) . In a randomized, placebo control trial, Fiatarone et al. (36) found that nutritional supplement alone failed to increase either muscle mass or muscle strength in the frail elderly. Moreover, the addition of nutritional supplements to ST did not increase muscle mass and muscle strength above the level achieved by ST alone (136, 137). Campbell et al. (136) found efficiency of retention and protein utilization during ST was higher in older subjects who consumed 0.8g vs 1.6g protein/kg/day of dietary protein, but the two different diet groups did not experience different muscle hypertrophy. Campbell's group (138) also compared the effect of meat containing diet with lactoovovegetarian on muscle mass changes under ST, and no difference was observed in the two groups regarding muscle mass and muscle size. However, Meredith et al (139) reported that a group taking energy-protein supplement (560 calorie surplus per day) gained significantly higher muscle mass without alterations in strength gained with ST than the group that had the same ST program, but without supplements. Thus, it appears that adequate energy intake rather than high protein intake has apparent additive effects on ST.

In addition, Volpi et al. (128, 140) suggested that makeup of nutritional supplements could affect the influence of supplements by showing that amino acids mixture actually stimulated muscle protein anabolism in older subjects. Those studies mentioned previously in this regard (36, 136, 137), all assigned subjects to a balanced meal consisting of protein, fat and carbohydrate. Volpi et al. (141) suggested that the addition of glucose may blunt the anabolic response of muscle to the stimulation of amino acid in the older adults. More longitudinal studies are needed to confirm

relationships between optimizing protein intake and preventing age-associated muscle loss.

The vitamin B6, magnesium and potassium were shown to relate to SM function in the elderly (142). However, reports on beneficial effects of multi-nutrient supplements on declining muscle mass and strength in the elderly could not be found.

Strength training. Because of the prevalence of sarcopenia and its adverse influences on the elderly, interventions designed for the prevention and treatment of sarcopenia should positively affect muscle mass, strength, and power without adverse side effects. For this reason, ST, rather than hormonal and nutritional interventions, should be the intervention of choice for sarcopenia, due to the substantial evidence for its efficacy within a very short time frame and for its safety (8, 143-145). Numerous investigations have shown the efficacy of ST to increase muscle mass and strength in older adults ranging from 50-98 years of age (143, 146-149). Additionally, the muscle adaptations in the elderly with ST have been shown to improve functional abilities (150).

Earlier work by Frontera et al (147) found that ST in older men leads to increased strength of the quadriceps with an increase in muscle fiber size. Since this data was published, numerous other investigations have been reported (32, 151-153) showing that muscle strength increases ~ 20 to 40% in response to ST in the elderly. This large range is at least partially due to study design differences. Problems arise when attempting to make comparisons between different ST studies, especially with different outcomes. First, studies vary greatly with regard to muscle group studied (e.g. upper body vs. lower body) as well as the volume (i.e. repetitions x sets) and

intensity (% of strength) used as an intervention. Furthermore, between-study comparisons are also problematic due to differences in the session frequency and duration of training interventions. Some report that improvements can be seen in as few as one session per week (154), while others used as many as seven sessions per week (155). The duration of ST interventions also vary considerably, with some lasting as little as four weeks (155) to almost two years (156), but most last between 8 – 12 weeks (157). Perhaps most importantly, the problem with comparing studies on the effects of ST interventions in older adults is the differences in subjects among the various studies. These variations include sex differences between groups, with some studies examining one sex, while other studies include both men and women (157). The ages of the study subjects can also vary significantly, with older subjects included ranging from those in their 50s to their 90s. In addition, subjects vary based on medical condition, medications, previous exercise experience, socioeconomic status, racial and genetic backgrounds. There is some evidence for a sex difference in muscle mass response to ST, as men increased quadriceps twice as much as women, after adjusting for baseline values (158). Although the majority of studies indicate that there is little age difference in muscle strength response to ST (157, 159), Lemmer et al. (160) reported an ~ 34% increase in strength in 20 – 30 year old men and women, which was significantly greater than the ~ 28% increase observed in 65 – 75 old subjects. These data suggest that in response to ST, skeletal muscle adaptations in older adults are comparable to the changes in younger adults. There are three general phases that occur in both young and older subjects that are responsible for strength increase during a ST program. First, during approximately

the first two weeks of a ST program, there is a strong learning effect that improves the subject's ability to perform the ST exercise. This phase of neurological adaptation results in improved coordination and rapid strength gains, especially if the strength training modality involves a high level of skill (157). This effect can often be attenuated by familiarization sessions, which can prevent observed strength gains from being inflated, especially in older adults. The next phase, which occurs at weeks ~ 3 – 7, involves increases in muscle strength without a concomitant increase in muscle mass. This improvement in strength is ascribed to continuing neural adaptations including increased activation of the agonist muscle group (i.e. increase motor unit (MU) recruitment and better coordinated MU firing), improved involvement of synergistic muscles, decreased antagonist muscle activation, and increased central nervous system (CNS) drive. Finally, the third phase of ST adaptations that occur at ~ 6 weeks and later results in increased strength along with a matching increase in muscle size.

Several training studies have reported muscle function changes with ST in older adults at the muscle fiber level. This data show that type I and type II muscle fibers in older adults maintain the ability to undergo hypertrophy with ST (58, 147, 161, 162), but some investigations found that there was only slight or no change in fiber areas (151, 163). Muscle quality (i.e. strength per unit of muscle mass) has been shown to improve with ST in older adults (32, 137, 148). For example, Tracy et al (32) reported a 14% and 16% increase in MQ in the quadriceps in response to a nine-week ST program for older men and women, respectively. More recently, Welle et al (137) examined the arm and thigh muscles of older women (62 – 72 yrs) and reported

that although aging might impair the hypertrophic response to ST, aging does not impair increases in MQ. In that study, older women increased their knee extensor MQ by ~ 32% which was similar to the ~ 38% change observed in younger women (137).

However, little is known about the effect of ST on fat infiltrating into aging muscle, such as LDM and the accumulation of IMF. For example, Sipila et al (9) assigned 18 weeks of full body ST to 76 to 78-yr-old women (n = 16) and induced a reduction in percent thigh IMAT with ST, but no information on change in absolute IMF was provided. The reduced percentage of fat may have just been due to the increase in thigh muscle mass, which lowers the percent of fat tissue, even if the total mass of fat doesn't change. Thus, there is a need for information on the actual change in IMF with ST. Cuff et al (10) compared the effect of combination of ST with AT (n =10) on LDM in 28 obese postmenopausal women training. The combination of ST with AT resulted in a reduction of mid-thigh LDM in comparison to control group. Janssen et al (11) studied the effect of 16-week long treatments: energy-restrictive diet with (n = 14) or without ST (n = 13), on mid-thigh IMF and observed a significant reduction in IMF in both groups. No differences were seen between diet alone and diet plus ST. Unfortunately, neither of these two studies can tell us the independent effects of ST on IMAT or LDM.

Genetics of ST Adaptation.

Muscle. 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 that ranged from 5 to 86 pounds (158). In the same study, the increase in quadriceps muscle volume ranged from 19 to 344 cm^3, and this accounted for an increase from <1% to about 20% of initial muscle volume. In addition, our group has reported muscle power changes with ST that are also quite variable (164). Others have also observed large variations in strength and muscle mass changes with ST. For example, Buchner et al. (165) reported one repetition maximum (1 RM) strength increases that ranged from 1 to 50 kg after 20 weeks of ST. The standard deviations of these changes were larger than the mean changes and the coefficients of variation (CV) were > 100 %. These data indicate that there are large inter-individual variations in muscle adaptation to even a very short term, highly standardized ST intervention.

These large inter-individual differences among older men and women are consistent with the possibility that genetic factors are involved in determining muscle adaptations to ST. Beisiadecki et al. (166) observed a 1.5 to 5.2 fold divergence between male rat with lowest muscle strength and highest muscle strength. Reed et al. (167) reported that genetic effects accounted for 65% of variance in grip strength, even after adjusting for the effects of height, weight and age. In addition, Seeman et al. (168) found that 60% to 80% of inter-individual differences in lean body mass could be explained by genetic factors. All of these data suggest the heredity plays an important role in skeletal muscle related phenotypes. The estimation of heritability of a specific trait is commonly estimated by twin and family studies. The most common analysis of heritability is phenotype measurement between and among sets of

monozygotic and dizygotic twins. If a trait was completely determined by genetics, there would be correlation of 1.00 between sets of monozygotic twins. 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 (169).

Evidence from heritability studies suggest that many skeletal muscle-related phenotypes, including strength, FFM, and skeletal muscle fiber composition are at least partially explained by genetic factors. 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. For example, Frederiksen et al. (170) reported that in 1,757 Danish twin pairs aged 45 - 96 years, that handgrip strength heritability is 52% and is 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. In addition, there was no significant influence of age or sex in this analysis, indicating that these variables were not confounders or effect modifiers. This heritability estimate is higher than previous data from postmenopausal female twins (171) that indicate a heritability estimate of 30%. 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% (172). A 10-year follow up indicated a heritability estimate of only 22% (172). More recently, Tiainen et al (173) indicated that handgrip and knee extension strength share a common genetic component, accounting for 14% of the

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

Muscle mass has also been investigated with regard to heritability using family and twin studies and it has been shown that estimates range from 50-90%. Data from an inbred founder population (Hutterites) with detailed family pedigree records indicates that FFM is highly heritable (h2 = 0.76) (174). In addition, Arden (171) indicated that in postmenopausal women, FFM has a heritability estimate of 56% when height and weight are covaried. This is somewhat lower than what Seeman et al (168) reported in younger female twins, who found that FFM is ~ 80% due to genetic factors. In addition, the estimation of FFM values has been shown to correlate more strongly among relatives than among unrelated individuals (175). More recent twin data confirm these estimates, finding a heritability estimate of 77% for FFM in both men and women (176). Age and sex do not appear to be significant covariates of within pair differences. Skeletal muscle fiber composition and enzyme activity are also heritable (177, 178). In order to more fully understand the specific contribution of specific gene variants toward explaining muscle phenotypes, an additional approach is to identify biologically plausible genes as a basis for conducting candidate gene association studies.

Roth et al (8) identified candidate gene polymorphisms associated with changes in strength and muscle mass with ST. They include angiotensin-converting enzyme gene (ACE), ciliary neurotrophic factor (CNTF), insulin-like growth factor I (IGF-1), IGF-II, tumor necrosis factors (TNF) alpha and vitamin D receptors. Although numerous cross-sectional or longitudinal studies have showed an association between these

genes and skeletal muscle mass and strength (179-185), the roles that these gene polymorphisms play in the determination of muscle adaptations to ST are still under investigation. Yet, there is limited information on how specific polymorphisms may affect muscle adaptation to ST. Folland et al. (186) reported that subjects with D alleles for the ACE gene gained greater strength than noncarriers in response to 9 weeks of ST; and this result was later supported by Colakoglu et al. (185), but not by Thomis et al. (187). Kostek et al. (149) from our group first reported carriers of 192 allele of IGF-1 gained significantly more strength with ST than noncarriers in response to a 10 week ST program. Our group has more recently found that a polymorphism of the alpha-actinin-3 gene (ACTN3) is associated with muscle power (188). Delmonico et al.(188) demonstrated that absolute change of power with ST was significantly higher in men with the RR polymorphism for the ACTN3 gene than those with XX, whereas, there was no difference in absolute power change among genotype groups in women at this locus. Another study from Clarkson et al. (189) found that those with ACTN3 XX gained greater strength than those with the RR polymorphism when adjusted for age and body mass. All of this available information and the results from future studies will help explain the genetic variations in muscle performances and adaptations to exercises.

Adipose Tissue. The interest in regional body fat has increased considerably because of its association with risk for various morbid conditions and mortality rate. Like the heritability of muscle, adipose tissue distribution and accumulation are heritable and affected by specific genes. Familial resemblance in body fat distribution has been reported (190). Bouchard et al. (175) also demonstrated that the genetic

effect on total body fat was about 25% and heritability of total energy content derived from fat mass and fat free mass was about 15%. Selby et al. (191) reported a significant genetic influence on central obesity basing on data obtained from 173 monozygotic and 178 dizygotic pairs of male twins using skinfold measurement. In the Canadian fitness study, Perusse et al. (192) found a 40% transmission effect across generations for trunk skinfolds and limb skinfolds . Bouchard et al. (175, 193) further studied data from the Quebec Family Study. After the influence of total fat mass was taken into account, subcutaneous fat mass was found to have a heritability reaching ~ 40 to 50% of the residual variance and visceral abdominal fat for heritability of ~ 56%. The influence of major genes on regional fat phenotypes were suggested in two studies (194, 195). Hasstedt et al. (194) defined a relative fat pattern index as the ratio of subscapular skinfolds thickness to the sum of the subscapular and suprailiac skinfold thickness; the 42 % of the variance of this index can be explained by genetic factors. The Quebec family studies (195) also reported that 35% of the variance in the trunk to extremity skinfolds ratio can be explained by genetic effects after adjusting for total fat mass. Thus, not only is adipose tissue heritable, but also the fat responses to interventions are significantly influenced by genetic factors. Bouchard et al.(196) conducted a series intervention studies with pairs of adult male identical twins to explain the genetic differences and outcome variations in the responses of body fat and regional body fat to interventions. In one study (197), 12 pairs of male homozygote twins showed considerable inter-individual differences in the adaptation to a 100 days of overfeeding (1000 calorie surplus per day). The variation observed was not randomly distributed because there were similar responses

within pairs. For example, the variance between pairs was three times more than the variance within pairs for the gain of fat mass. The results were similar even in response to a short term overfeeding period (198). In another study, Bouchard et al. (199) had seven pairs of male identical twins run on cycle ergometers twice a day out for 10 days over 93 days, while consuming a constant daily energy intake and nutrient intake. A daily 243 MJ energy deficit was created on average. There were large inter-individual responses to this exercise protocol. However, the intrapair resemblance was still observed for body weight, body fat, percent body fat, sum of skinfolds and abdominal visceral fat measured by CT. Those with the same genotypes responded to exercise interventions more similarly than those with different genotypes, particularly for body fat, abdominal visceral fat. Altogether, these data clearly show a genetic influence on body fat response to interventions.

It is well established that there is a large inter-individual variation in body fat responses to aerobic exercise training. Monozygotic adult twin studies (199) revealed that genetic factors influence adaptations of body fat to aerobic exercise training. A number of studies have demonstrated significant associations of specific gene variations (polymorphisms) with the magnitude of body fat loss induced by aerobic training (14, 15, 25, 200, 201). For example, the Heritage family study (25) showed that white women with the adrenergic receptor (ADR) beta Arg16Arg genotype had a greater reduction in fat and percent fat in response to aerobic training, while results were mostly negative in blacks. Marcho-Azcarate et al. (14) reported ADR beta2 Glu27Glu groups had higher plasma TG levels and respiratory quotient than the Gln27Gln group. Thus, lipolysis and fat oxidation seemed to be blunted in the

Glu27Glu group in response to aerobic training. Phares et al. (15) observed collective effects of different ADR gene polymorphisms on the responses of body fat to exercise training.

Despite the absence of ST effects on IMF and LDM, few studies showed the ST-induced reductions in total body fat (22), abdominal subcutaneous fat and visceral fat (23, 202). Trueth et al. (22) observed significant loss of total fat mass and mid-thigh subcutaneous fat after 16 week ST in older men. In another study, Treuth et al. (23) observed a reduction in intra abdominal adipose tissue without change in total body fat in fourteen healthy older women after 16 weeks of ST. Hunter et al. (202) observed the effect of 25 weeks of full body ST in older men and women. While women significantly lost intra abdominal adipose tissue and abdominal subcutaneous adipose tissue, men did not lose either of these two fat mass significantly with ST. In a randomized controlled trial, Binder et al (203) reported that total fat, truck fat, intra-abdominal and abdominal subcutaneous fat did not change significantly with 6 months of ST in frail older adults compared to a control group. Because there was no information in the literature on the effects of ST on intermuscular fat (IMF) and low density muscle (LDM), which appears to have important health implications, we initially addressed this issue in a pilot study involving 12 middle-aged and older participants of this study. We found a reduction in IMAT with ST, but with a large inter-individual variation, as 9 subjects lost IMAT (from 2.2cm 2 to 24.8 cm2), whereas 3 subjects actually gaining IMAT after training. A similar large inter-individual variation was also seen in the adaptation of LDM. These preliminary data suggested that the adaptation of fat to ST may be influenced by genetic factors.

The influence of ADR and ADR polymorphisms on lipid metabolism.

Based on the previous investigations on aerobic exercise training and its influence on adipose tissue metabolism, ADR gene polymorphisms seem to be a top candidate to explain genetic influences.

Adrenergic receptors (ADRs) are the protein expressed in the plasma membrane of adipocytes. They are the receptors for catecholamines (epinephrine and nonepinephrine) and therefore principally control the lipolysis. Catecholamines activate the lipolytic cascade by binding to ADR β1, β2 and β3, whereas catecholamines binding to ADRα2 inhibits lipolytic activity. These ADRs interact with GTP-binding regulatory protein (G proteins) which modulate the activities of adenylate cyclase (AC) enzyme. All of the ADR β1, β2 and β3 are coupled with stimulatory G protein (Gs) while ADRα is coupled with inhibitory G protein (Gi). The activation of AC by ADR β receptors result in the conversion of ATP to cAMP. cAMP is a second messenger to activate cAMP-dependent protein kinase, which then phosphorylates hormone sensitive lipase (HSL) and perilipins (204). HSL and perilipins then break down triglycerides into free fatty acids and glycerol. Thus, the biological responses of catecholamines, at least partially depend on the functional balance between ADRβs and ADR α2 receptors. For example, both genders have a lower lipolytic response to catecholamines in femoral and gluteal adipocytes than in subcutaneous adipocytes because the latter shows increased ADRβ density and sensitivity and reduced ADRα2 number and affinity (205-207). Human and animal studies showed that a shift to higher ADR α2 / β ratio contributed to obesity and net lipid storage (208).

ADRβ2 may be the only ADRβ receptors involved in TG metabolism in skeletal muscle. Ligget et al. (209) demonstrated a dominant expression of ADRβ2 in skeletal muscle using a ligand binding technique. Hagstorm-Toft and her colleagues (13) utilized a microdialysis technique to observe ADRβs regulation of lypolysis in skeletal muscle in healthy subjects. Nonspecific ADRβs blocker or specific ADRβ2 blocking agent was found to counteract the induced lipolysis and ADRβ1 blocking agents did not affect glycerol release at all. Moreover, the perfusion of β2-selective agonist induced concentration dependent increase in skeletal muscle glycerol release, whereas perfusion of β1 and β3 agonist did not result in any change in glycerol release. Thus, in skeletal muscle, ADRβ2 is the only important receptor for the regulation of lipolysis.

There exists marked large interindividual variability in the physiological responses to ADRs agonists and antagonists as well as functions and expressions of ADRs (210). This suggests genetic factors are involved in explaining variability in ADRs among human populations. Because of their principal and interacting roles in the regulation of lypolysis and because of our special attention to fat metabolism in skeletal muscle, the influences of ADRβ2 and ADRα2 polymorphism on fat distribution, accumulation and adaptation to interventions will be reviewed in the subsequent section

ADRβ2 gene polymorphisms. ADRβ2 gene has three polymorphisms, including Thr164Ile, Gln27Glu and Gly16Arg (211). Thr164Ile is a rare variant with minor allele frequency among populations of only about 2 to 5%. The homozygous individual was never found in the population suggesting this variant may be lethal.

When minor alleles Ile164, Glu27 and Arg16 substitute major alleles Ile164, Gln27 and Gly16, respectively, the function of ADRβ2 is markedly changed in recombinant cells (29, 212). For example, ADRβ2 Ile64 decreased high-affinity agonist binding, ADRβ2 Glu27 decreased agonist-promoted down-regulation and ADRβ2 Gly16 promoted agonist-promoted down-regulation (210). However, the cell culture-based analysis may not provide for the environment necessary to assess relevance of a polymorphism in an intact human.

A number of clinical studies have showed the influences of ADRβ2 in fat distribution. Large and his colleagues (77) investigated a group of 140 women with large variation in body mass index (BMI). Gln27Glu polymorphism was found to be markedly associated with obesity. Homozygotes Glu27 had an average excess fat mass of 20 kg and ~ 50% larger fat cells than noncarriers (Gln/Gln). However, Gly16Arg was not significantly associated with obesity. When Large et al. (213) extended the study to non-related male subjects with a large range of BMI (213), the differences in fat phenotypes disappeared among ADR β2 Gln27Glu carriers, suggesting a potential gender-specific effect of Glu27 on fat mass. In the IRAS (insulin resistance and atherosclerosis) family study, Lange et al. (24) studied African-American (AA) and Hispanic American (HA) from three different geographical sites and measured subcutaneous and abdominal fat with CT. The Glu27 allele was found positively associated with body mass index, visceral adipose tissue, but not with subcutaneous adipose tissue. The Arg16Gly polymorphism was not associated with any of the measures of adiposity, which is consistent with the finding reported by Large et al (77). The HERITAGE family (25), however, reported

that Glu27 allele carriers have lower fat accumulation in obese men than noncarriers. And among white obese women, Gly16Gly carriers had a lower fat accumulation than other genotype carriers (Arg16Gly and Arg16Arg), whereas this association was negative in black women. It is not clear what causes the discrepancy in the relationship between ADRβ genotypes and fat phenotypes.

The ADRβ2 polymorphisms not only influence fat distribution, but also the adaptation of fat to either overfeeding (214) or aerobic training (14, 15). Ukkola et al. (214) fed 12 pairs of identical twins a 4.2 MJ / day energy surplus for a period of 100 days, and found that the ADRβ2 Gln27Gln carriers gained more weight and total subcutaneous fat than the Glu27Glu and Gln27Glu genotypes, whereas there was no significant difference in fat mass distribution among ADRβ3 genotype carriers. Macho-Azcarate et al.(14) observed higher TG, lactate level and respiratory quotient after aerobic training in Glu27Glu group than in Gln27Gln group. Moreover, Phares et al. (15) reported that Glu27 carriers lost a greater percent total body fat and trunk fat than noncarrers in response to a 24- wk aerobic training program. In the HERITAGE family study (25), white women with Arg16Arg genotype exhibited a greater reduction in fat mass and percent fat mass than other genotypes carriers (Arg16Gly, Gly16Gly).

ADRα2b polymorphisms. There were three known subtypes of ADRα, α2a, α2b and α2c. These three subtypes were encoded by distinct genes located in different chromosomes. ADR α2a has a relatively uncommon SNP which was predominantly found in African Americans and has been found to be associated with salt-sensitive hypertension in the African American population (215). The ADRα2c also has a

polymorphism 10 times more common in African Americans. Heinonen et al. (78) first identified a polymorphism in the third loop of in ADR α2b receptor: a deletion of 3 glutamic acids from a glutamic acids repeat element, resulting in three genotypes i.e. Glu12/Glu12, Glu12/Glu9 and Glu9/Glu9. In the same study, the measured basal metabolic rate adjusted for fat-free mass, fat mass, sex and age was lower in those carrying Glu9/Glu9. Lower metabolic rate was known as a risk factor for obesity (216). Sivenius and his colleagues (217) then investigated the effects of ADRα2b polymorphisms on the change of body weight in 126 non-diabetic Finnish during a 10 year follow-up. The non-diabetic subjects with Glu9/Glu9 had a greater increase in their mean body weight during 5 yr follow-up than those subjects with the any other genotypes. The increment of body weight in Glu12/Glu9 carriers was significant. However, The ADR Glu12/Glu9 polymorphism was not significantly associated with body weight in type 2 diabetics cross-sectionally or longitudinally. Dionne et al. (218) genotyped 909 unrelated Caucasian women with a wide range of BMI and did not find any significant differences in fat mass and visceral fat between Glu12/Glu9 carriers. However, those carrying both ADRα2b Glu9 and ADRβ3 Arg 64 had a 9.8 kg and 4.8% greater fat mass than ADRβ3Arg 64 only carriers.

The effect of a single ADRα2b polymorphism on the adaptation of fat to interventions has not been reported, but the interacting effects with other ADRβ genotypes have. Phares et al. (15) reported that in response to aerobic training, Glu12/Glu12 carriers who also carried Arg64 of ADRβ3 exhibited a significantly greater loss in percent total body fat, percent trunk fat and fat mass than all other ADRα2b and ADRβ3 genotypes combined. The impact of ADRβ3 polymorphism on

training-induced body composition change, however, is not a consistent finding. For example, Garenc et al. (219) found no relationship between ADR β3 genotypes with the responses to exercises in the HERITAGE family study. However, the interacting effect between ADR α2b and ADRβ2 on the fat adaptations to exercises is impressive. As a result of aerobic exercise training, ADRα2b Glu9 noncarriers who also carried ADRβ2 Glu27 showed two to four times more reduction in percent trunk fat, and two times more reduction in total fat mass than any other ADRα2b and ADRβ2 genotypes combined (15).

Summary and Conclusions.

In summary, sarcopenia is the age-associated loss of muscle mass and muscle strength with adverse effects on health status and functional abilities in the elderly. The increasing fat infiltration into the muscle with aging, as indicated by the development of low density muscle (LDM) and intermuscular fat (IMF), may be an important aspect of sarcopenia because of its association with declines in muscle strength, reduced leg performances, rises in mobility limitations, and increased insulin resistance. Because of the prevalence of sarcopenia and the detrimental effects on quality of life in the elderly, several interventions have been tried to slow and reverse the loss of muscle mass and strength in the elderly, such as hormonal intervention, nutritional supplement and strength training. In this regard, strength training is considered the intervention of choice for the prevention and treatment of sarcopenia because of its effectiveness and safety. Strength training can induce the reduction of total body fat and abdominal visceral fat (22, 23, 202). However, little or no information on the effect of strength training on low density muscle and

intermuscular fat is reported in the literature. It is well known that muscle adaptation to strength training is variable and this variation can be partially explained by specific gene polymorphisms. Preliminary data from our group showed similar variability for fat adaptation to strength training.

Adrenergic receptors play a principal role in the regulation of lipolysis and the balances between the stimulatory (ADRβs) and inhibitory receptors (ADRα2b) determine the efficacy of lipolysis induced by catecholamines. Moreover, ADR gene polymorphisms are considered candidate genes of choice for investigating their influence on fat phenotypes in response to interventions, such as regular exercise. The associations between ADRs polymorphisms and the adaptation of fat mass to aerobic training have been reported and the results suggest the need to address this relationship with strength training as an intervention for sarcopenia. Therefore, there is a need to investigate the effects of strength training on low density muscle and intermuscular fat, and investigate the association between this effect and specific ADR polymorphisms, such as ADRβ2 Gln27Glu and ADRα2b Glu12 / Glu9.

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