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DETERMINANTS OF INTRA-INDIVIDUAL VARIATION IN ADAPTABILITY TO RESISTANCE TRAINING OF DIFFERENT VOLUMES WITH SPECIAL REFERENCE TO SKELETAL MUSCLE PHENOTYPES

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Determinants of intra-individual variation in adaptability to resistance training of different volumes with special reference to skeletal muscle phenotypes

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Abstract

The preface pretty much says it all.

Second paragraph of abstract starts here.

List of scientific papers

I. **Hammarström D**, Øfsteng S, Koll L, Hanestadhaugen M, Hollan I, Apró W, Blomstrand E, Rønnestad B, Ellefsen S Benefits of higher resistance-training volume are related to ribosome biogenesis. The *Journal of physiology.* 2020;598(3):543-65.

II. Khan Y, **Hammarström D**, Rønnestad B, Ellefsen S, Ahmad R Increased biological relevance of transcriptome analyses in human skeletal muscle using a model-specific pipeline. *Submitted.*

III. **Hammarström D**, Øfsteng S, Jacobsen N, Flobergseter K, Rønnestad B, Ellefsen S Ribosome accumulation during early phase resistance training. *Manuscript*

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1. Introduction

Skeletal muscle health is essential for physical independence. In a lifespan perspective, measures of muscle mass and/or strength are inversely associated with mortality (1–6) and disability (7). Besides adverse associations between of low muscle mass and strength and clinical conditions, muscle weakness also accounts for increased health care costs in patient populations (8,9). The intercept between muscle mass, muscle function and health status is interrelated with variables such as age and primary illness or injury (10). This highlights that interventions designed to increase muscle mass and strength are likely to prevent adverse health outcomes across the lifespan. A higher level of muscle mass and functional capacity would counteract the effects of muscle loss due to illness, age or inactivity.

Although a large degree of the observed variations in lean mass and strength are attributed to genetic components (11,12), environmental factors also contribute, leaving a window of opportunity to increase muscle mass and functional capacity. Among factors affecting muscle mass and functioning are nutrition and pharmacological agents. However, physical activity and specifically systematic resistance training of sufficient volume, intensity and frequency provides a stimulus that promote morphological and functional changes to the human neuromuscular system without adverse side-effects. Irrespective of age, resistance training generally leads to increased muscle mass and strength (13,14) and is considered safe when performed in a well organized manner (14,15).

Resistance training can be modulated indefinitely through combined variations of training variables such as frequency, intensity and volume (16,17). Well designed training prescriptions should incorporate information about the current state and goals of the trainee to maximize the potential outcome of the training program (16–18). Training volume has received particular attention in the scientific community for many reasons. Evidence suggests that exercise volume affects selected molecular determinants of muscle hypertrophy in a dose-dependent manner (19–21). Such effects are believed to facilitate long-term training effects as training programs with higher volume generally result in higher gains in muscle mass and strength with little evidence of differences between age groups or participants with different training backgrounds (22–24).

A consequence of a more extensive training program is the increased time required to complete such a program. As time constraints has been reported as a limiting factor for engaging in physical activity (25) some merit can be given to arguments against guidlines suggesting higher volume in resistance training prescription (18,26). From an individual perspective, training prescription that balances time-requirement with efficacy presumably increases the likelihood of participation in physical activity (25). From a more general perspective, increased knowledge about mechanisms governing responses to physical training could improve training prescription also for individuals and populations that experience attenuated benefit of resistance training (27). The overreaching goal of the present thesis is to contribute to understanding individualized training loads. To this end, training volume was used to study the effects of variable training stimulus in within-participant models of exercise-training.

2. Background

2.1 Effects of resistance exercise volume on muscle strength and mass

Precise exercise-training[1] prescription gives information on exercises, their sequential order, intensity and volume at which exercises should be performed, rest periods between efforts or sessions and the frequency at which exercise sessions are to be performed (23). By manipulating these variables, resistance training programs can be tailored to better fit goals and starting points of any individual. The relative importance of exercise-training variables for training outcomes has been examined in numerous studies including (but not limited to) the overall organization of exercise sessions, (28,29) training frequency (30), and intensity (31). It could be argued that training volume is of particular importance for muscle growth as when this variable is held constant, manipulation of other variables has little or no effect hypertrophy (31,32). For development of strength, factors such as intensity and within session organization of exercises is of importance (33,34), however, when other factors are held constant, increased training volume generally leads to increased strength (22,33,35), similarly to effects of training volume on muscle growth (23,24).

Exercise volume can be prescribed as the within session number of sets performed per muscle group. This unit is practical as it comparable between individuals and muscle groups (36). Berger conducted an early study concerning effects of resistance exercise volume with the goal to determine what method most efficiently produced strength gains (in healthy young males) (37). Berger compared one, two and three sets performed with two, six or ten repetition maximum (RM) in the bench press, three times per week, over twelve weeks. As the combined

[1] Exercise is herein defined as an acute bout of physical activity designed to affect physical characteristics such as strength, speed or endurance. Training is defined as the systematic process of combining multiple exercise-sessions performed in sequence over time. Resistance-exercise is defined as an acute strength-promoting program requiring the neuromuscular system to exert force against resistance. Resistance training is defined as a long-term process of multiple resistance exercise-sessions performed over a defined period of time.

effect of three sets per session was superior regardless of the number of repetitions performed Berger concluded in favor of three sets. This conclusion was later challenged on the basis of data interpretation (18,26). Reveiwing the study by Berger and others, Carpinelli and Otto arrived to the conclusion that there was "insufficient evidence to support the prevalent belief that a greater volume of exercise (through multiple sets) will elicit superior muscular strength or hypertrophy" (26). This stand has since been repeatedly put forward as a criticism of higher volume training programs (38,39) and sparked considerable scientific activity. The main argument against the recommendation of additional volume in strength training programs has been the lack of statistically significant results in single studies (18,38). Indeed, individual studies do not generally agree on dose-dependent effects of training volume on muscle mass and strength gains (40–51), including studies performed within participants, where different training volumes are allocated to either extremity (52,53). For example, differences in strength are between volume conditions are found in older individuals (40,41,46) but not confirmed in another study (44)]. Studies shows that more volume does not lead to increased muscle gains in young individuals (42,47,49) a conclusion challenged by others (43,51).

As previously noted, combining the above results and additional studies, meta-analyses concluded that training volume dose-dependency exists for the development of muscle mass and strength [(33); (35); (22); (23,24). As a second argument against additional volume in resistance training recommendation has been the cost/benefit relationship of adding training volume without meaningful or substantial additional gains (18,38), a subsequent question is, whom would benefit from greater volumes and whom would not? Schoenfeld *et al.* combined data from published studies to explore if participant characteristics of the above mentioned studies interacted with training volume in explaining study outcomes. Neither sex, muscle groups nor age interacted with volume prescription indicating that no such factor would be able refine training prescription guidelines (24). As the number of studies used to synthesis the meta-analysis was relatively low ($n = 15$) and the studies were heterogeneous in terms of e.g. outcome measurements, it may have lacked in power to detect any meaningful interactions. Additionally, included studies may not have been reporting relevant characteristics for such analysis.

Collectively, the available evidence suggest that there is overlap between training outcomes in studies were different volume has been utilized. The overlap cannot, with available data, be explained by general population characteristics such as age or sex. Studying the effect of different training volumes within participants could potentially help to define determinants of training outcomes in response to different volume conditions. Two within-participant studies have investigated the effects of training volume on strength and hypertrophy outcomes. Sooneste *et al.* compared strength outcomes in response to three- and one-set elbow flexor training for 12 weeks in young males using a whitin-participant protocol (arms allocated to either volume condition). The results showed general benefit of three- over one-set training for muscle hypertrophy and tended to do so also for strength gains (53). No attempts were made to relate baseline characteristics to the magnitude of differences between volume conditions, presumably due to the small sample size ($n = 8$). Mitchell *et al.* compared muscle hypertrophy and strength gains in response to three- and one-set of knee-extension exercise performed three times per week for ten weeks. The study contained an additional training condition (low intensity, 30% of 1RM performed with three sets) with participants legs assigned to either of the three conditions in a random fashion. No significant differences were reported between volume conditions for muscle mass or strength gains (52). However, the analyses were performed without taking the correlation between individuals into account due to the mixed design (52). No attempts were made to relate any measured characteristic to differences in responses.

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3. Aims

The primary aim of this thesis was to relate the adaptive response to resistance training with low- and moderate-volume to skeletal-muscle characteristics in previously untrained individuals. The key question was whether manipulation of exercise-volume will have diverse effects in different individuals related to muscular intrinsic characteristics. A further aim was to characterize exercise-volume dependence in muscle molecular characteristics and determine a time course profile of markers of ribosomal biogenesis in response to resistance training. Based on these aims, the objectives of the present thesis were;

- to relate skeletal muscle and systemic characteristics to benefit of moderate- compared to low-volume resistance training;
- To determine volume-dependence in molecular networks related to muscle growth and remodeling in response to resistance training
- To determine a time course of markers related to ribosome biogenesis in the early phase of resistance training.

4. Methods

4.1 Study participants, protocols and training interventions

Study I was designed to examine effects of low- and moderate-volume on responses to acute exercise and long-term training within participants. Forty-one healthy individuals were recruited and 34 of these completed at least 85% of the prescribed sessions and were thus included in subsequent data analyses. Reasons for not completing the trial included injury not related to the study ($n = 1$), pain or discomfort during exercises ($n = 5$) and non-adherence to the study protocol. There were no differences in characteristics between participants included in or excluded from data analysis in Study I.

Study II was designed to study the effects of resistance training *per se*, and effects of variable volume on selected markers related to ribosome biogenesis. Participants were therefore recruited to a training group ($n = 11$) and a non-training control group ($n = 8$). Eligible for participation in both studies were young (Study I age 18-40; Study II 18-35), non-smoking men and women. Exclusion criteria included a training history of more than one weekly session during the last 12 (Study I) or six (Study II) months leading up to the study. Participants were also screened for intolerance to local anesthetic, current or previous injuries affecting their ability to perform resistance training, self-reported symptoms or history of disease, intake of medication or supplements with known effects on adaptations to training. Participant characteristics for both studies are shown in Table 4.1.

4.2 Resistance training interventions

Each training session started with a light standardized warm-up (5 min ergometer cycling and 10 repetitions each of push-ups, sit-ups, back-extensions and squats). Before each exercise in the main program, one set of 10 repetitions were performed in the specific exercise with approximately 50% of 1RM.

Table 4.1: Participant characteristics

		Sex	Age (years)	Stature (cm)	Mass (kg)	Fat mass (%)	Lean mass (%)
Study I	Included	Female	22.0 (1.3)	168 (7)	64.4 (10.4)	34.1 (5.6)	64.3 (6.2)
		Male	23.6 (4.1)	183 (6)	75.8 (10.7)	20.4 (6.0)	79.3 (5.0)
	Excluded	Female	22.9 (1.6)	166 (8)	64.6 (9.7)	28.8 (8.7)	68.6 (9.1)
		Male	24.3 (1.5)	189 (5)	88.2 (22.4)	24.3 (15.3)	76.8 (12.7)
Study II	Training	Female	23.4 (2.9)	168 (8)	64.0 (9.2)	30.8 (7.1)	65.5 (6.8)
		Male	25.7 (5.8)	177 (3)	77.5 (8.0)	25.3 (3.9)	71.3 (2.4)
	Control	Female	24.1 (3.5)	166 (4)	63.8 (0.6)	30.5 (6.4)	66.3 (5.2)
		Male	25.5 (5.5)	182 (5)	76.5 (7.7)	18.2 (5.1)	78.7 (4.2)

Data are means and (SD)

Studies were fully or partially performed as within-participant studies as each participant had their legs assigned to different training conditions (not including the control group in Study II). Allocation was performed after enrollment where each participant had their legs randomized to either low- or moderate volume (Study I), or variable or constant volume (Study II).

In Study I, the low-volume protocol consisted of a single set of each exercise and the moderate-volume consisted of three sets per exercise. Three unilateral leg exercises were used (leg press, leg curl and knee extension). The moderate volume-leg commenced all sessions and the low volume-leg performed a single set of each exercise in the rest between second and third set of the moderate volume training protocol.

In Study II, only unilateral knee-extension was performed in an effort to concentrate the stimulus to the quadriceps muscles. The constant-volume leg performed six sets of 10RM throughout the study and variable leg performed six sets in session one to four, three sets in session five to eight and nine sets in session nine to twelve with same intensity (10RM).

4.2.1 Ethical considerations

Both studies were approved by the local ethics committee Lillehammer University College/Inland Norway University of Applied Sciences and the Norwegian Centre for Research Data. In accordance with the *Declaration of Helsinki*(54) the studies were pre-registered in publicly accessible databases (Study I, ClinicalTrials.gov Identifier: NCT02179307; Study II, `https://osf.io/wa96y`). Participants were informed of the study design, potential risks and sources of discomfort prior to giving their informed consent.

4.3 Muscle tissue sampling and preparations for downstream analyses

Muscle samples were obtained under local anesthesia (Study I, Xylocaine, $10\,\mathrm{mg\,ml^{-1}}$ with adrenalin $5\,\mathrm{\mu g\,ml^{-1}}$, AstraZeneca, Oslo, Norway; Study II, Lidocaine Mylan, $10\,\mathrm{mg\,ml^{-1}}$, Mylan Ireland Ltd, Ireland) with a fine needle (12-14 gauge; Universal-plus, Medax, Italy) operated with a spring-loaded instrument (Bard Magnum, Bard Norway AS, Norway). Sampling was performed as previously described (55), with modifications. Anesthesia was injected in the subcutaneous tissue with care taken not to inject anesthesia into the muscle itself. Following pilot experiments we decided not to use an insertion cannula as described in (55) as the biopsy needle itself could be used to puncture the skin and muscle fascia. This also resulted in less discomfort. Several passes through the same skin puncture was made to obtain sufficient material for downstream analyses. A smaller needle (14 vs. 12 gauge) was used to further minimize discomfort in Study II where more biopsies were sampled over a shorter time span, with exception from when material was used for immunohistochemistry. The first biopsy was sampled at one third of the distance between the patella to the *anterior superior iliac spinae* with subsequent biopsies sampled $\sim$2 cm proximal to previous samples. In Study II, samples obtained more than one week apart were sampled with closer proximity and distally from previous samples but never at previous sampling sites.

The micro biopsy technique produces smaller samples compared to other biopsy techniques (56), and thus requires several passes to produce sufficient material for multiple downstream experiments. However, reports confirms that the micro biopsy technique is comparable to the traditionally used Bergström technique in several measures of muscle characteristics at the same time as being well tolerated (55,57). Any reported differences in fiber type distributions between sampling techniques have been suggested relating to differences in sampling depth (57,58).

For determination of fiber type distributions, a threshold of 200-300 fibers has been suggested as a suitable sample size per specimen as more fibers does not reduce the variation between dupliacte samples (59). In Study I, one or several pieces of muscle (total weight $\sim$15 mg) were chosen per sampling for analysis of fiber type distributions (described in detail below). The total number of fibers were counted from these specimens (Figure ref fig). Using an average of fibers from the first sampling time point the between leg coefficient of variation was determined to 14% for Type I fibers and 11.3 for type II fibers. The between leg variation in Type I fibers is similar to what has been previously reported…

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5. Results and Discussion

5.1 Effects of different training volume on changes in muscle size and function

In Study I, the average increases (Table 5.1) in muscle strength and mass in each volume condition corresponded to what could be expected based on previous studies (13,60).

Average within participant differences in responses between LOW and MOD were consistent across measures of muscle hypertrophy and strength gains (Figure 5.1). These differences were in agreement to what could be expected based on published meta-analyses (22–24,35). Taken together, these observations confirmed the efficacy of the training program in general and a dose-response with regard to within-session exercise volume.

In Study II, training efficacy was assessed by comparing outcomes to a non-training control group. The training group displayed increases compared to the control group for both strength muscle thickness measures.

Table 5.1: Training induced changes in muscle CSA and average strength in Study I

	Sex	Volume condition	Mean (SD)	Reference
CSA %-change	Female	LOW	3.05 (3.61)	
		MOD	5.02 (4.04)	
	Male	LOW	3.83 (3.50)	
		MOD	5.10 (3.71)	
CSA %-change day	Female	LOW	0.04 (0.05)	0.11 [0.04-0.26]a
		MOD	0.07 (0.05)	
	Male	LOW	0.05 (0.05)	
		MOD	0.07 (0.05)	
CSA %-change session	Female	LOW	0.11 (0.13)	0.08 (0.22)b
		MOD	0.18 (0.15)	
	Male	LOW	0.14 (0.12)	0.14 (0.14)b
		MOD	0.19 (0.13)	
Average strength %-change	Female	LOW	21.0 (9.8)	
		MOD	27.8 (14.4)	
	Male	LOW	19.2 (12.4)	
		MOD	23.1 (12.0)	
Average strength %-session	Female	LOW	0.77 (0.36)	0.67 (0.35)b
		MOD	1.00 (0.49)	
	Male	LOW	0.72 (0.48)	0.47 (0.22)b
		MOD	0.87 (0.46)	

[a] Estimates from Wernbom et al. (60)
[b] Estimates from Ahtiainen et al. (ref:ahtiainen-citation

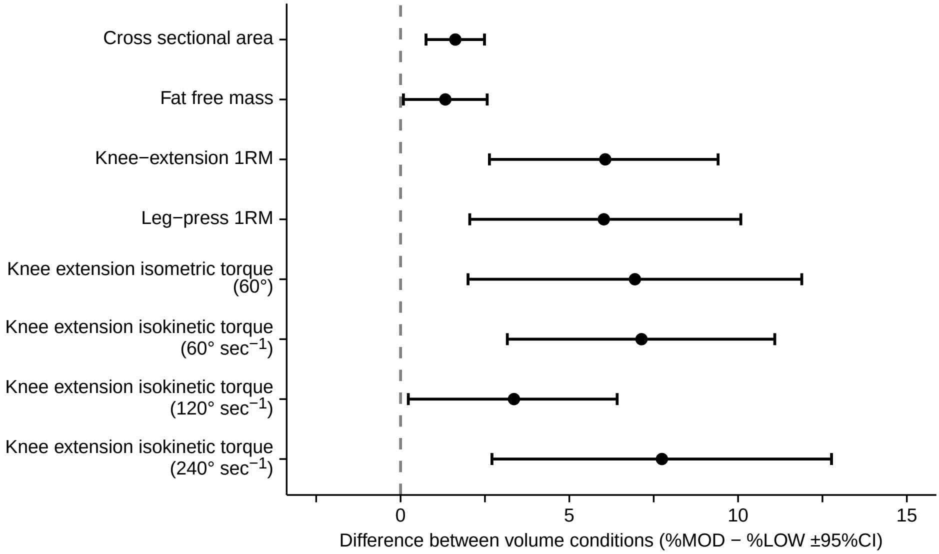

Figure 5.1: Differences in training induced relative changes in muscle mass and strength measures. Estimates are derived from ANCOVA models controling for baseline values and sex.

5.2 Acute effects of diffrent training volume on determinants of muscle protein synthesis

6. General Discussion

Conclusion

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More info

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