# SKELETAL MUSCLE ADAPTATIONS TO LOW-LOAD RESISTANCE EXERCISE COMBINED WITH BLOOD FLOW RESTRICTION IN OLDER ADULTS WITH KNEE OSTEOARTHRITIS

By

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To my family

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LIST OF ABBREVIATIONS

| | |
|---|---|
| 1RM | One-repetition maximum |
| $^{31}$P-NMR | $^{31}$Phosphatate nuclear magnetic resonance spectroscopy |
| BFR | Blood flow restriction |
| CAF | C-terminal agrin fragment |
| CI | Confidence interval |
| CNTRL | Control group (traditional exercise) |
| DBP | Diastolic blood pressure |
| DEXA | Dual-energy x-ray absorptiometry |
| ELISA | Enzyme-linked immunosorbent assay |
| EMG | Electromyography |
| GH | Growth hormone |
| IGF-1 | Insulin-like growth factor 1 |
| K/L | Kellgren-Lawrence grading scale |
| KOOS | Knee Osteoarthritis Outcome Score |
| LLFDI | Late Life Function and Disability Instrument |
| MAPK | Mitogen-activated protein kinase |
| MMSE | Mini-mental State Exam |
| mTOR | Mammalian target of rapamycin |
| OA | Osteoarthritis |
| P3NP | N-terminal peptide of procollagen type III |
| SBP | Systolic blood pressure |
| SMD | Standard mean difference |
| SPPB | Short Physical Performance Battery |

| | |
|---|---|
| TWEAK | Tumor necrosis-like weak inducer of apoptosis |
| VAS | Visual analog scale |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

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Skeletal muscle weakness is a primary contributor to pain, functional decline and disease progression among older persons with knee osteoarthritis (OA). Thus, resistance exercise is commonly used as a preventative and rehabilitative intervention in this population. High-load resistance exercise performed with >60% of one-repetition maximum (1RM) is the best-known intervention for improving skeletal muscle strength. However, persons with OA may be unable to perform high-load exercise due to pain and joint compression. As a result, interventions are needed that are capable of increasing strength while utilizing low loads. One potential strategy is the addition of blood-flow restriction (BFR) to low-load training. This strategy is effective for increasing skeletal muscle strength relative to low-load training alone in healthy adults. Thus, the objective of this randomized, single-masked pilot trial was to evaluate the efficacy and feasibility of BFR training for improving skeletal muscle strength and physical function among older adults with knee OA. A total of 30 participants aged ≥60 years with symptomatic knee OA were randomly assigned to twelve weeks of center-based,

traditional resistance exercise (CNTRL, 60% 1RM to volitional fatigue) or BFR (20% 1RM). Study outcomes included changes in 1) 1RM  2) isokinetic knee extensor strength 3) objective (Short Physical Performance Battery (SPPB), 400m walk) and subjective measures of physical function (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Late Life Function and Disability Instrument (LLFDI)) 4) body composition 5) gait parameters and 6) serum markers of muscle hypertrophy. Changes in 1RM and isokinetic knee extensor strength were not statistically significantly different between groups (time*condition interactions $p>0.05$) but tended to favor the CNTRL intervention. Similarly, changes in 400m walk and subjective function as assessed by LLFDI tended to favor the CNTRL intervention, whereas changes in WOMAC stiffness favored the BFR intervention.  Changes in SPPB and gait parameters were similar between groups. Furthermore, changes in total lean mass, fat mass and body fat percentage tended to favor CNTRL. Serum P3NP was significantly higher in CNTRL relative to BFR, while serum IGF1 was similar between groups. Serum TWEAK tended to be lower CNTRL relative to BFR. Finally, P3NP demonstrated moderate to strong correlations with eccentric knee extensor force characteristics, while TWEAK was positively associated with 400m walk speed and negatively associated with changes in body fat. These findings indicate that the CNTRL intervention tended to be more efficacious for strength and function in persons with knee OA. However, results should be interpreted with caution as this trial was not fully powered to detect differences in these outcomes.

# CHAPTER 1
# INTRODUCTION

The primary purpose of this project was to fill critical gaps in our understanding of how resistance training combined with mild blood flow restriction to the working muscles (BFR) influences skeletal muscle hypertrophy among older adults with knee osteoarthritis. *These data provide information critical to our long-term goal of evaluating the efficacy of BFR training for improving physical function among clinically-relevant populations.*

High-load resistance exercise (~ 60% of maximal strength) is the best known intervention for improving skeletal muscle strength and hypertrophy.[1] As a result, resistance exercise is strongly recommended for a wide range of clinical populations, particularly those with the greatest risk of disablement due to declines in skeletal muscle mass and function.[2] Unfortunately, many of these populations--such as frail older adults, and those with musculoskeletal disorders such as osteoarthritis (OA)--are typically unable to perform resistance exercise with optimal loads due to pain, fatigue, or a lack of self-efficacy.[3] Consequently, current recommendations include the performance of low- or moderate-load resistance exercise—despite the fact that these training paradigms are sub-optimal for improving skeletal muscle function. Therefore, alternative interventions are needed for improving skeletal muscle strength while utilizing low loading paradigms.[4]

Low-load resistance exercise performed with blood flow restriction (BFR) is superior to low-load resistance exercise alone for improving skeletal muscle strength and hypertrophy,[5] and in some cases BFR may be comparable to high-load training for this purpose[6] Therefore, BFR is an attractive alternative training paradigm for

populations in which high-load exercise is contraindicated. Prior studies have demonstrated that BFR exercise induces skeletal muscle hypertrophy under a variety of conditions, including alone or in combination with exercise not typically shown to induce skeletal muscle growth (e.g. walking[7,8]). While the exact mechanisms are unclear, BFR is thought to induce these changes through multiple mechanisms including metabolic stress, cell swelling and increased skeletal muscle activation.[9] Recent evidence suggests that BFR may have benefits for bone and joint health as well, [10] further increasing its potential value for persons with OA.

To date, the majority of BFR studies have utilized healthy young adults, with few examining older adults and scarcely any evaluating older adults with chronic health conditions. In addition, the majority of these studies are short-term (<6 weeks) and few data exist regarding functional outcomes. As a result, relatively little is known about the potential efficacy of BFR as a therapeutic intervention among older adults with chronic conditions such as OA. Furthermore, to our knowledge, no study to date has examined the molecular mechanisms underlying the effects of BFR exercise in older persons with OA (e.g. skeletal muscle growth pathways, neuromuscular activation, cartilage and bone turnover, inflammation). These markers will be critical for optimizing the dosage (exercise load, volume, cuff width and pressure) and determining the safety of BFR exercise for persons with OA. Therefore, the overarching objective of this work was to evaluate, amongst a clinically-relevant population, the molecular mechanisms underlying skeletal muscle adaptations to chronic BFR training.[4]

We evaluated these adaptations in 30 participants from a recently completed, NIH-funded trial comparing the efficacy of BFR to traditional resistance training among

older adults (≥ 60 years) with knee OA. Our central hypothesis was that 12 weeks of BFR training would beneficially alter concentrations of serum markers indicative of chronic skeletal muscle adaptations, and these adaptations would be associated with improvements in objective and subjective measures of skeletal muscle strength and function. We leveraged the existing resources and infrastructure of the recently completed trial to address the gaps in the current literature by assessing the skeletal muscle adaptations to 12 weeks of BFR (20% 1RM) to those of high-intensity resistance training (CNTRL, 60% 1RM) according to the following aims:

**Aim 1. To determine the extent of change in serum biomarkers of skeletal muscle hypertrophy and function in response to BFR and HIRT**

We used commercially-available enzyme-linked immunosorbent assay (ELISA) kits to determine serum concentrations of the following biomarkers from serum collected at baseline, week six and week twelve of the trial.

**Insulin-like growth factor-1 (IGF-1):** Increases with resistance training and is associated with increased protein synthesis and lean mass.[11]

**Tumor necrosis-like weak inducer of apoptosis (TWEAK):** Associated with inflammation and skeletal muscle regeneration.[12] Lower TWEAK expression is associated with skeletal muscle hypertrophy and greater force production.[13]

**N-terminal peptide of procollagen type III (P3NP):** Product of the formation of skeletal-muscle specific isoform of collagen. Serum P3NP expression is positively associated with changes in lean body mass.[14]

**C-terminal agrin fragment (CAF):** Product of agrin cleavage. Agrin is produced by neurons and stimulates acetylcholine receptor clustering at the neuromuscular

junction. High serum concentrations of CAF are associated with poorer physical function.[15]

**Aim 2: To assess changes in clinically-relevant gait parameters in response to the training interventions**

During ambulation, skeletal muscle acts to reduce shock and provides stability to the joints.[16] Skeletal muscle weakness results in an inability of the muscle to counteract the external forces placed on the joint during movement which may contribute to OA disease initiation and progression. Additionally, a number of gait abnormalities have been identified in persons with OA and are thought to be associated with OA disease severity.[17] In particular, persons with OA demonstrate slower overall step cadence, shorter step length and reduced single-leg stance time relative to healthy counterparts. These and other gait abnormalities are associated with reduced lower-extremity strength[18] and greater pain and physical disability[19] among persons with OA. Therefore, we evaluated these gait parameters at baseline, six and twelve weeks using the GAITRite® system (GAITRite, Franklin, NJ).

**Aim 3: To determine if observed training-derived changes in serum biomarkers are significantly associated with changes in strength, physical function and skeletal muscle mass**

Skeletal muscle weakness is one of the earliest manifestations of OA, and is more closely associated with physical disability among persons with OA than pain or joint space narrowing.[20] As skeletal muscle size a major determinant of skeletal muscle strength, we hypothesized that serum biomarkers of skeletal muscle hypertrophy would be associated with changes in lean mass and physical function. Physical function was

objectively assessed using walking speed over 400m, the Short Physical Performance Battery (SPPB), and knee extensor strength measured at 60 degrees/s, 90 degrees/s and 120 degrees/s. Subjective measures of pain and physical function were assessed using the Late Life Disability and Function Instrument (LLFDI) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Lean mass was determined using dual-energy x-ray absorptiometry (DEXA). We correlated these variables and the GAITRite® analysis (Aim 2) with the change in serum biomarkers in response to the intervention.

# CHAPTER 2
# LITERATURE REVIEW

## Background

Osteoarthritis (OA) is one of the most common musculoskeletal disorders and is a leading cause of disability among older adults.[21,22]Estimates indicate that up to 80% of older adults ≥65 years show radiographic evidence of OA in at least one joint,[22] with hand, knee and hip joints being the most commonly affected. Pain due to OA--particularly of the hip and knee—is strongly associated with the incidence of physical disability.[23-25] Given the increasing prevalence of OA and rapid aging of the population, OA-associated disability among older adults is a growing public health concern.[26,27]

Skeletal muscle weakness represents an important modifiable risk factor that is a primary contributor to the exacerbation of OA and its symptoms.[28,29] As a result, physical activity designed to increase skeletal muscle strength is often used in rehabilitation and management of OA. Indeed, increased skeletal muscle strength is associated with reduced pain and improved physical function and quality of life among persons with OA.[30,31] To maximize gains in skeletal muscle strength, resistance exercise performed with a heavy external load (>60% of one-repetition maximum) is considered to be most effective.[1,32] However, training with high compressive loads may not be feasible for many persons with OA due to potential exacerbations of joint pain and lack of self-efficacy.[33] Therefore, alternative training strategies are needed capable of improving skeletal muscle strength while utilizing low loads.

One potential strategy is the use of blood-flow restriction (BFR) in combination with low-load exercise. Blood-flow restriction is achieved through the use of a pressure cuff placed proximal to the working skeletal muscles. In brief, the pressure cuff is

inflated during exercise so that arterial flow is turbulent while venous return is mildly restricted.[34,35] Prior studies have demonstrated that BFR exercise is capable of increasing skeletal muscle hypertrophy and strength.[5] However, to date, the majority of BFR studies have utilized healthy young adults, with few examining older adults and scarcely any evaluating older adults with chronic health conditions. As a result, relatively little is known about the potential efficacy of BFR as a therapeutic intervention among older adults with chronic conditions such as OA. As such the purpose of this review is to examine the extant evidence related to the potential for using BFR exercise as a therapeutic intervention for preserving skeletal muscle strength and function among older adults with osteoarthritis.

## Literature Search Methodology

The National Library of Medicine (PubMed) database, the Cochrane Database of Systematic Reviews and Web of Science were used to search for relevant articles, and reference lists were reviewed for additional relevant articles. Specific search terms used alone or in combination were: ‘osteoarthritis,’ ‘blood flow restriction,’ ‘vascular occlusion,’ ‘kaatsu,’ ‘transient ischemia,’ ‘intermittent hypoxia,’ ‘physical activity,’ ‘aerobic,’ ‘resistance,’ ‘exercise,’ ‘weight training,’ ‘mechanical loading,’ ‘skeletal muscle,’ and ‘activation.’

## Skeletal Muscle Function and OA

Skeletal muscle weakness is a common clinical feature of OA patients.[36,37] Weakness of the knee extensors and flexors in particular is associated with hip and knee OA. Although a direct relationship between skeletal muscle weakness and OA disease initiation and progression in humans has not yet been elucidated,[38] increased strength is associated with a reduction in pain and improved physical function and

quality of life among persons with OA.[31,39-42] In addition, skeletal muscle strength may modulate several peripheral causes of pain and disease progression associated with OA, including joint space narrowing,[43] gait abnormalities,[44,45] and joint loading during ambulation.[46,47] Skeletal muscle size may also play a role, as muscle cross-sectional area is related to muscle force production.[48] Indeed, longitudinal data suggest that thigh muscle volume is positively associated with knee cartilage volume and negatively associated with cartilage volume loss over two years of follow-up.[49] As a result, interventions capable of increasing skeletal muscle size and strength (e.g. resistance training) are likely to benefit persons with OA.

Skeletal muscle weakness is one of the earliest manifestations of OA, and is more closely associated with physical disability among persons with OA than pain or joint space narrowing.[20,50] Aside from acute injury, cartilage degeneration of the weight bearing joints is thought to largely result from excessive chronic joint loading.[51,52] During ambulation, skeletal muscle acts to reduce shock and provides stability to the joints.[16,53] Skeletal muscle weakness results in an inability of the muscle to counteract the external forces placed on the joint during movement which may contribute to OA disease initiation and progression.[53] Additionally, a number of gait abnormalities have been identified in persons with OA and are thought to contribute to joint degeneration.[17,54] One of the most studied measures is the external knee adduction moment, which is often used as a proxy for medial knee compartment loading during ambulation.[55] However, a number of studies have failed to show an association between increased quadriceps strength and reductions in the knee adduction moment during walking.[56-59]

Thus, a direct role of skeletal muscle weakness in OA disease initiation and progression in humans is yet to be established.[38]

Still, studies utilizing a rabbit model of Botulinum toxin A-induced quadriceps weakness provide evidence that skeletal muscle weakness leads to cartilage degeneration independent of gait biomechanics.[60,61] Furthermore, Leumann and colleagues[62] demonstrated that skeletal muscle weakness induced changes in knee structural tissue mRNA expression of collagens I and III and matrix metalloproteinases 1, 3, and 13, thus providing evidence that skeletal muscle weakness results in altered metabolism of joint tissues in rabbits.[62] In humans, evidence for the role of skeletal muscle weakness in OA comes primarily from observational studies. Persons with OA display concentric quadriceps strength deficits of 11-56% relative to aged-matched healthy controls.[63] Skeletal muscle weakness in persons with OA is primarily caused by reduced muscle mass and/or reduced muscle activation secondary to pain, anxiety, neural inhibition and altered joint biomechanics.[64] A meta-analysis of studies using electrical stimulation to elicit maximal contraction of the quadriceps found activation deficits of approximately 20% in the involved and contralateral limbs of persons with OA relative to healthy controls.[65] Local anesthesia is capable of improving skeletal muscle activation by ~12%, suggesting that pain or fear of pain is a major contributor to muscle activation deficits in persons with OA.[66]

Skeletal muscle atrophy also likely contributes to skeletal muscle weakness among persons with OA. Hart et al. [67] found that quadriceps volume was ~10-15% lower among persons with OA relative to aged-matched controls. Similar deficits of 12% were reported by Ikeda et al.[68] when comparing women with OA to age-matched

controls and by Petterson et al. [69] when comparing muscle volume between the involved and uninvolved limbs of persons with unilateral OA. Furthermore, Fink et al.[70] obtained biopsies from the vastus medialis of persons with OA undergoing knee replacement surgery and found evidence of type II muscle fiber atrophy (defined as fiber diameter <30 µm in females or <40 µm in males) in all participants studied. Longitudinal data suggest that an increase in skeletal muscle cross-sectional area from baseline to two years was associated with a decreased risk of joint replacement surgery at two and 4.5 years.[71] Due to the proposed benefits of improving skeletal muscle function (size and strength) in persons with OA, exercise training is a cornerstone of rehabilitation and management of the disease.

## Efficacy of Exercise for Management of OA

Indeed, numerous studies indicate that exercise training is efficacious for persons with OA. Various forms of exercise including strength training, aerobic training, water-based exercise and tai-chi all appear to reduce pain and disability among persons with OA.[31,42,72-78] For example, Juhl et al.[74] analyzed results from 47 trials and 4028 patients and found that regardless of training modality, exercise training significantly reduced pain (standard mean difference [SMD] 0.50, 95% CI 0.39-0.62) and disability (35 trials, 2732 patients, SMD 0.49, 95% CI 0.35-.063). These effects equated to a 9% (95% CI 7-11%) reduction in pain and an 8% (95% CI 6-11%) reduction in physical disability according to self-assessment using Visual Analog Scales (VAS). Similar results were reported in a recent Cochrane review of exercise interventions for knee OA. In this analysis, exercise training resulted in a 12% (95% CI 10-15%) reduction in pain and a 10% (95% CI 8-13%) reduction in perceived physical disability relative to non-exercise controls.[31]

Although sufficient evidence exists to show exercise training is capable of reducing pain and improving physical function in OA, it is less clear which training modalities are most effective. Meta-analyses comparing the effects of resistance and aerobic exercise on pain and physical disability among persons with OA were equivocal, with some showing greater efficacy of resistance exercise[74] and others showing no difference.[73] It is also unclear whether combined training improves outcomes relative to aerobic or resistance training alone, as some analyses concluded that combined training was less effective for improving pain[74,75] and physical function,[74] while another showed combined training (resistance, flexibility, and land or water-based aerobic exercise) to be more effective.[72] As a result, published guidelines for exercise in the management of OA vary considerably in terms of recommended training modalities. However, low-impact aerobic exercise, resistance exercise, and flexibility training are often recommended.[79]

For improving skeletal muscle strength, high-load exercise appears to be more effective than lower-load exercise modalities in persons with OA.[78,80] A recent meta-analysis by Zacharias et al.[80] compared low-load resistance exercise to non-exercise controls (10 studies, 768 participants) and found evidence for small increases in knee extension strength at short-term follow-up (6-13 weeks, Standard Mean Difference [SMD] 0.47, 95% CI 0.56-0.92) but no significant effect at intermediate-term (20-24 weeks, SMD 0.08. 95% CI -0.16-0.32) or long-term follow-up (>24 wks, SMD 1.05, 95% CI -1.02-3.12). However, this group found moderate effect sizes for increased knee extension strength following high-load resistance exercise relative to non-exercise controls at short-term (4 studies, 195 participants, SMD 0.76, 95% CI 0.47-1.06) and

long-term follow-up (3 studies, 129 participants, SMD 0.80, 95% CI 0.44-1.17).[80] Similarly, a recent Cochrane review comparing high-load exercise to low-load exercise found a significant effect size for overall lower-body strength favoring high-load exercise (SMD 1.01, 95% CI 0.74-1.27).[81] However, while heavy loads may be optimal for improving skeletal muscle size and strength and reducing OA symptoms, these loads are not always well tolerated among persons with OA.[82] Thus, alternative strategies such as BFR combined with low-load exercise may be warranted in persons with OA.

**Skeletal Muscle Adaptations to BFR Exercise**

Blood flow restriction is capable of improving skeletal muscle size and strength when combined with exercise, even with loads and exercise modalities not typically associated with such improvements (e.g. low-load resistance exercise,[83-86] walking[7,8]). The mechanisms by which BFR augments the adaptive response to low-load exercise are not completely understood. However, several recent reviews detailed the possible molecular mechanisms,[9,34,87,88] which include local and systemic hormone release, increased motor unit recruitment, increased muscle protein synthesis and decreased protein degradation secondary to metabolic stress and cellular swelling.

Metabolic stress—characterized by increased blood lactate concentration, inorganic phosphate accumulation, lowered intramuscular pH and phosphocreatine depletion—is a primary signal for skeletal muscle hypertrophy following resistance exercise.[89] High metabolic stress, specifically an increase in blood lactate concentration, is associated with an increase in post-exercise testosterone[90-92] and growth hormone (GH) synthesis and release.[90,93,94] Exercise with BFR (160-230mmHg, 20-40% 1-RM) increases lactate concentration and intramuscular inorganic phosphate while lowering pH relative to low-load exercise alone,[95-99] and induces similar acute metabolic stress

relative to high-load exercise (65% 1-RM).[97] Subsequently, BFR exercise increases systemic GH expression relative to low and high-load exercise without BFR. However, most studies show no change in total testosterone, [7,100-102] free testosterone[100,103] or IGF-1[102-104] following BFR exercise. Furthermore, the relationship between post-exercise changes in systemic hormone expression and muscle hypertrophy is still under debate[105,106,107] leading to speculation that other factors are primarily responsible for signaling skeletal muscle growth in response to BFR training.[9,35]

Metabolic stress may also mediate the skeletal muscle hypertrophic response following BFR by increasing cellular swelling. Accumulating metabolites—particularly lactate[108]--create an osmotic gradient favoring fluid flow into the cell. This increase in cellular hydration is thought to activate growth signaling pathways[109] (e.g. mammalian target of rapamycin [mTOR] and mitogen activated protein kinase [MAPK]) and inhibit proteolysis[110,111] secondary to mechanical stretch of the sarcolemma, [112] ultimately resulting in a net increase in protein synthesis. Cellular swelling may also stimulate skeletal muscle hypertrophy by increasing activation and proliferation of skeletal muscle satellite cells.[113] Although many of these molecular responses are augmented by the addition of BFR to low-load exercise,[114-117] it should be noted that a recent investigation by Gundermann et al.[118] failed to show an increase in skeletal muscle protein synthesis or mTOR and MAPK signaling using a pharmacologically-induced increase in post-exercise blood flow. However, the peak pharmacologically-induced post-exercise blood flow and plasma lactate concentrations were lower relative to BFR exercise. Thus, the pharmacological increase in post-exercise blood flow may not have been sufficient to mimic the physiological responses to BFR exercise. Further studies are needed to

elucidate the role of cellular swelling in stimulating skeletal muscle hypertrophy following BFR exercise.

Blood flow restriction may also augment the hypertrophic response to low-load exercise by increased activation of type II motor units secondary to hypoxia and metabolic stress.[9,87,119,120] Low-load exercise performed under normal conditions is generally not a sufficient stimulus to activate higher-threshold (type II) motor units.[121] However, BFR exercise (130% SBP, 20% 1-RM) is capable of stimulating similar type II fiber activation relative to higher-load resistance exercise (65% 1-RM) as measured by $^{31}$Phosphatate nuclear magnetic resonance spectroscopy ($^{31}$P-NMR).[95,122] As Type II skeletal muscle fibers have a higher capacity for hypertrophy than type I fibers,[123] this increased activation of type II fibers is a possible mechanism for augmented skeletal muscle growth with BFR exercise. Furthermore, BFR exercise (100-160mmHg, 20% 1-RM) increases skeletal muscle activation relative to low-load exercise alone as measured peripherally[124-126] (surface electromyography [EMG]) and centrally.[127] Given the activation deficits typically seen in persons with OA, this may be an important mechanism for skeletal muscle strength gains and improvements in physical function with BFR exercise. However, it should be noted that some studies failed to show an increase in skeletal muscle activation with BFR exercise relative to work-matched low-load exercise without BFR[128,129] or low-load exercise performed to volitional fatigue.[130] Furthermore, Cook et al. demonstrated that high-load exercise (70% peak torque) elicited greater skeletal muscle activation relative to low-load exercise (20% peak torque) performed to volitional fatigue and BFR exercise (20% peak torque, 180mmHg).[130] However, although the neuromuscular adaptations to BFR exercise may

be dissimilar to higher-load resistance exercise, BFR exercise may still be beneficial for persons with OA due to a reduced capacity to train with heavier loads or to maintain sufficient output to reach volitional fatigue.

**Recent Studies Relevant to BFR Exercise for OA**

Despite the possible benefits of BFR combined with low-load exercise, to our knowledge only three studies to date have utilized this exercise modality for persons with or at risk for OA. Segal et al.[131] compared low-load intensity exercise (30% 1-RM ) with or without BFR (65mm-wide cuff inflated to 160-200mmHg) in 45 women aged 45-65 years (average age 54.6±6.9 yrs control group and 56.1±5.9 yrs BFR) with at least one risk factor for symptomatic knee OA. Risk factors included 1) body mass index ≥25kg*$m^{-2}$ 2) history of knee joint injury or surgery 3) pain, aching or stiffness on most of the last 30 days 4) being told that they have radiographic knee OA. Participants had not participated in resistance training during the last three months. The exercise intervention consisted of bilateral leg presses performed three times per week over four weeks. Outcomes included bilateral leg-press isotonic strength and power, stair climb power, and knee pain (Knee Osteoarthritis Outcome Score, KOOS). Additionally, a subset of participants (n=6 from each group) were randomly selected for analysis of quadriceps muscle volume measured by MRI. Both groups significantly improved in leg press 1-RM strength and stair climb power relative to baseline. The BFR group also significantly improved on leg press power assessed at 40% of 1-RM and isokinetic knee extensor torque relative to baseline. The increase in knee extensor torque was significantly different from the control group (-0.05±0.03 Nm/kg control vs. 0.07 ±0.03 Nm/kg BFR, p=0.0048). Knee pain and quadriceps volume were unchanged relative to baseline in both groups.

In a separate study, Segal et al.[132] used a similar protocol to assess the effects of low-load exercise and BFR in 42 men aged 45-90 years (average age 56.1±7.7 yrs). Outcomes included isotonic leg press strength, isokinetic knee extension strength at 60°/s and knee pain (KOOS). Following the exercise intervention, leg press 1-RM was significantly improved in both groups relative to baseline (4.7±1.3%, $p<0.002$ control, 3.1±0.9%, $p=0.003$ BFR), but was not significantly different between groups ($p=0.322$). Isokinetic knee extensor strength was only improved relative to baseline in the control group (6.7±2.3%, $p=0.062$ control vs. 0.4±2.4%, $p=0.883$ BFR, $p=0.066$ between groups). Neither group improved KOOS scores following the intervention (14.2±7.2%, $p=0.062$ control vs. 4.9±3.3%, $p=0.155$ BFR).

Finally, Bryk et al.[133] compared high-load resistance exercise (70% 1-RM) to low-load resistance exercise with BFR (30% 1-RM, cuff pressure 200 mmHg, cuff width not reported) in 34 women (average age 60.4±6.7 yrs control vs. 62.3±7.0 yrs BFR) with diagnosed knee OA based on American College of Rheumatology criteria. Participants had a K/L grade score of two or three in one of the knees. Exclusion criteria included previous surgery or invasive procedure on the affected knee, previous physical therapy, participation in any knee strengthening program. The training program combined flexibility (static hamstring stretches) and sensorimotor training (standing on a mini-trampoline) with midsection and lower-body strengthening exercises. The primary exercise was seated knee extensions (3 sets of 10 repetitions with 70% 1-RM for control, 3 sets of 30 repetitions at 30% 1-RM for BFR). The exercise intervention was performed three times per week for six weeks. Outcomes included quadriceps maximum isometric voluntary contraction, anterior knee pain assessed during exercise

and at the pre/post-intervention, and physical function (Lequesne functional scale and timed up-and-go). Both groups improved significantly relative to baseline in isometric strength, physical function and knee pain, Although not statistically significant, the magnitude of isometric quadriceps strength gain tended to be greater following BFR (+42% for BFR vs. +30% for control). Furthermore, the BFR group reported less anterior knee pain during exercise relative to the control group (p=0.01), indicating that low-load exercise combined with BFR may be better tolerated than high-load exercise in this population.

## Conclusions and Perspectives

Resistance training may reduce pain and improve physical function secondary to improved skeletal muscle function in persons with OA. However, a number of factors including joint pain and diminished self-efficacy may limit the performance of resistance exercise with optimal loads. Resistance exercise combined with BFR is capable of improving skeletal muscle function while utilizing low-loads. As a result, exercise with BFR is a promising alternative intervention for management of OA as well as other clinical conditions in which skeletal muscle function is compromised – including inflammatory myopathies,[134,135] ligament[136] and bone[137] injury rehabilitation, and sarcopenia.[85,138]

Although BFR exercise holds considerable promise for management of OA, there are several knowledge gaps in the current literature that will need to be addressed in future trials. To our knowledge, no study to date has examined the molecular mechanisms underlying the effects of BFR exercise in persons with OA (e.g. skeletal muscle growth pathways, neuromuscular activation, cartilage and bone turnover, inflammation). These markers will be critical for optimizing the dosage (exercise load,

volume, cuff width and pressure) and determining the safety of BFR exercise for persons with OA. Furthermore, recent evidence suggests that there is significant molecular cross-talk between skeletal muscle and other joint structures,[139] suggesting that exercise may directly modulate OA disease progression. Indeed, exercise alters cartilage expression of many genes associated with inflammation and cartilage metabolism. [140] Moreover, intermittent hypoxia also reduces inflammation in synovial tissues,[141] suggesting that the addition of BFR may further modulate the inflammatory response compared to resistance exercise alone. This may be of particular importance for early OA disease management.[142] While speculative, future research on the direct disease-modifying effects of BFR exercise may be warranted.

While BFR exercise has many potential advantages over traditional high-load resistance exercise for persons with OA, there are several limitations. Logistically, BFR exercise requires considerable investments in equipment and technical expertise. Also, while BFR exercise is generally well tolerated, certain parameters (cuff pressure, cuff width) may influence perceived exertion and discomfort. These issues may potentially limit widespread applicability. Additionally, BFR can only be applied to the limb musculature. As a result, supplementary training for proximal and midsection muscle groups may be necessary to maximize the benefits of BFR exercise. In conclusion, BFR exercise appears to be a promising alternative to high-load resistance exercise among older adults with OA, however well-controlled studies identifying the mechanisms of action as well as investigating the clinical viability are needed.

# CHAPTER 3
# METHODOLOGY

## Research Design

The purpose of this study was to evaluate the skeletal muscle adaptations to 12 weeks of resistance exercise either with (BFR) or without BFR (CNTRL) among older adults with knee osteoarthritis. This study was an ancillary study utilizing a subset of participants from a randomized, single-masked pilot trial designed to evaluate the safety and efficacy of BFR exercise for improving physical function among older adults with symptomatic knee osteoarthritis. Prior to randomization in the study, interested individuals participated in an initial screening visit to determine eligibility (Table 2-1). This included a review of medical history, physical activity habits, medication use, and the Mini-mental State Exam[143] to ensure participants had normal cognitive function (MMSE ≥ 24). Following these procedures, the 400 m walk test[144] and Short Physical Performance Battery (SPPB)[145] were performed as well as a medical exam that included assessment of OA-related symptoms.

## Participant Characteristics

Data from a total of thirty previously sedentary adults aged ≥60 years were included in the present analysis (n=14 BFR, n=16 CNTRL). Eligibility criteria are listed in Table 3-1. Briefly, eligible participants had objective signs of functional limitations (SPPB score ≤10 or walking speed <1.2 m/sec), had OA of the knee defined by (1) radiographic evidence of osteophytes, (2) pain classification > grade 0 on Graded Chronic Pain Scale, (3) and bilateral standing anterior-posterior radiograph demonstrating Kellgren and Lawrence grade >1 of the affected knee. Persons with contraindications to tourniquet use, including those with peripheral vascular disease,

systolic blood pressure (SBP) >160 or <100 mm Hg, diastolic blood pressure (DBP) >100 mm Hg, absolute contraindications to exercise training,[146] or with other medical conditions that would preclude safe participation were excluded. All participants provided written informed consent before randomization, and all study procedures were approved by the University of Florida Institutional Review Board.

## Interventions

Participants in each study arm performed center-based resistance exercise three days per week throughout the 12-week study period (36 total sessions). Following a brief warm-up (stationary cycling or walking), participants performed machined-based lower-body strength exercises followed by a brief cool-down routine consisting of balance exercises and stretching. Resistance exercises--leg press, leg extension, leg curl and calf extension-- were performed using standard resistance training equipment (Life Fitness, Schiller Park, IL). Participants performed three sets on each machine with a one-minute rest between sets and five minutes of rest between machines. All exercises were performed to volitional fatigue--defined as the inability to complete a pain-free range of motion after strong verbal encouragement. Ratings of perceived exertion were obtained following each set using the modified Borg scale (0-10).[147] Participants in the CNTRL exercise group performed the resistance exercises at an intensity of 60% of one-repetition maximum (1RM) according to exercise guidelines for seniors with OA.[1,146]

For the KAATSU intervention, resistance exercises were performed using 20% of 1RM with external compression applied to the proximal thigh of each leg. Compression was applied according to published tourniquet guidelines[148] and maintained by

pneumatic cuffs (TD 312 calculating cuff inflator, Hokanson, Bellevue, WA). Cuff pressure was set according to the equation [pressure=0.5*(SBP)+2*(thigh circumference)+5].[149] Cuffs remained inflated during performance of each exercise (i.e. between sets) but were deflated for five-minute rest periods between exercises. All exercise sessions were supervised by trained and American Heart Association Basic Life Support-certified exercise interventionists.

Load was adjusted based on subsequent RM testing at week three, week six and week nine. To determine 1RM, participants performed brief general warm-up and subsequently completed 4-6 sets of each exercise with a progressively increasing load. Participants then performed as many repetitions as possible and 1RM was calculated[150] according to the formula 1RM load*(1.0278-(0.0278*repetitions))$^{-1}$.

## Study Outcomes

### Skeletal Muscle Strength

Participants performed muscle strength testing on both limbs at baseline, week six and week twelve. Maximal isokinetic strength of the quadriceps extensors was assessed using a Biodex-System 3 (Biodex Medical Systems, Inc., Shirley, NY). Participants performed three submaximal trial repetitions of seated leg extensions at an estimated effort of 25%, 50%, 75% and two maximal (100% effort) repetitions followed by a rest period of one minute. Subsequently, participants performed five maximal (100% effort) repetitions at 60 degrees/s, 90 degrees/s, and 120 degrees/s. Finally, participants completed an endurance protocol consisting of 50 repetitions at 120 degrees/s. Outcomes obtained included 1) average peak torque (N*m) 2) average power (W) and 3) average total work (N*m).

Participants also completed 1RM testing for each machine used for the training intervention at baseline and week 12. Following a brief general warm up, participants completed 4-6 sets of each exercise with a progressively increasing load. Participants rested for ~3 minutes between sets. Load was increased until the participant could only perform one repetition through the full range of motion, and this load was determined to be 1RM.

**Measures of Functional Status**

Functional outcomes included usual-paced gait speed measured during a 400 m test and performance on the SPPB (Table 3-2). These tests have high clinical relevance, as they have proven reliable and valid for predicting adverse health outcomes among seniors.[151-154] During the 400m walk test, participants were asked to complete 10 laps around a 40m course. Time and distance walked were recorded, and gait speed was determined in m/s. For the SPPB, participants performed a timed standing balance test, a four-meter walk, and a repeated chair stand. A score ranging from zero (inability to complete the task) to four (best performance) was recorded for each test, and the scores were summed for a final score ranging from 0-12.

**Gait Analysis**

Gait analysis was performed at baseline and week twelve using the GAITRite® system. This system employs an 8-m long mat equipped with fifteen sensor arrays. The system recorded location of activated sensors and time of activation/deactivation during a self-paced walk test. The walk test was repeated six times and the values of specific parameters were averaged for the six trials. GAITRite® software was used to examine the gait parameters. Gait parameters collected included 1) velocity (cm/s) 2) velocity normalized to leg length (leg length/sec, leg length measured from greater trochanter to

the floor, bisecting the medial Malleolus 3) step cadence 4) step length differential (left:right ratio) 5) step time differential (elapsed time from first contact of one foot to first contact of opposite foot) 6) cycle time differential (elapsed time between first contacts of two consecutive steps of same foot) 7) single leg support stance time (time elapsed between last contact of current footfall to first contact of next footfall of the same foot) and 8) toe in/toe out angle (angle between line of progression and midline of the foot). .

**Self-Assessed Pain and Physical Function**

The WOMAC is a multidimensional, self-administered functional-health status instrument for patients with lower limb OA.[155] The WOMAC index is a 24-item questionnaire divided into three subscales, which measure pain (WOMAC-pain; 5 questions), stiffness (WOMAC-stiffness; 2 questions), and physical function (WOMAC-function; 17 questions). Each question is rated on a 0-4 scale, with 0 indicating no difficulty performing the task and 4 indicating extreme difficulty. The WOMAC total score was the sum of the three subscale scores. The WOMAC has demonstrated validity as well as sensitivity to treatment effects in patients with knee pain.[156,157]

The Late Life Function and Disability Instrument (LLFDI) includes 16 tasks representing a broad range of disability indicators that assesses both frequency of doing a task and perceived limitation. The instrument uses a scale from 0 to 100, with higher scores indicating higher levels of function. The scale has strong concurrent and predictive validity with physical performance.[158]

**Body Composition**

Body composition was assessed at baseline and week twelve using dual energy x-ray absorptiometry (DEXA) (Hologic, Waltham, MA). Outcomes assessed included 1) android/gynoid ratio (%fat waist/%fat hip) 2) total mass 3) fat mass 4) total lean mass

(muscle and soft organ tissue) 5) total bone mineral content (BMC) and 6) body fat percentage.

**Serum Biomarkers**

Bood was collected from the antecubital vein according to standard laboratory practices at baseline, week six and week twelve. Serum was separated by centrifugation and stored at -80°C for later analysis. Serum levels of insulin-like growth factor-1 (IGF-1, R&D Systems, Minneapolis, MN), tumor necrosis-like weak inducer of apoptosis (TWEAK, R&D Systems, Minneapolis, MN), N-terminal peptide of procollagen type III (P3NP, MyBioSource, San Diego, CA), and C-terminal agrin fragment (CAF, Neurotune, Zurich, Switzerland) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Concentrations of each target protein were determined using the colorimetric method at an optical density of 450 nm with a microplate reader (Biotek, Winooski, VT). Standard curves were generated using a commercially available microplate reader-compatible statistical software (Biotek Gen5, Winooski, VT). These standard curves were generated for all measures using commercially developed standards with specific antigens with reported r values in the range of 0.948-0.999. Intra-assay coefficients of variation for each assay were determined for each duplicate for all participants and resulted in a mean coefficient of variation of 3.4%.

For TWEAK, a spike-recovery control experiment was performed according to manufacturer instructions to validate the kit for use with human serum. Briefly, two 1-mL aliquots of serum sample were prepared. One 980µL aliquot was spiked with 20µL of kit standard TWEAK concentrate (20 ng/mL) and the other aliquot was analyzed without spiking. A control sample was prepared by adding 20 µL of TWEAK standard to 980 µL

of the supplied reagent diluent. These samples were serially diluted in reagent diluent (neat, 1:2, 1:4, and 1:8) and analyzed relative to the standard curve. Spike-recovery was determined as % Recovery = Observed value (pg.mL) x 100/(Expected value (pg/mL)/dilution factor), where “observed value” refers to the spiked sample value and “expected value” refers to the control spiked sample value. Linearity was determined as % Recovery (dilution) = Observed value (pg/mL) *100/Expected value (pg/mL)*dilution factor. All values for spike-recovery and linearity were within the acceptable range of 80-120% (%Recovery = 99.8%, linearity 88.9-95.9%), indicating that the TWEAK ELISA kit is valid for analysis of human serum.

**Statistical Analyses**

Repeated measures analysis of covariance (ANVOCA) was used to determine differences in mean outcome measures between intervention groups. Baseline outcome measure, age, gender, baseline pain rating on the visual analog scale and the intervention group assignment were included in the model. Hypothesis tests for intervention effects at assessment visits were performed using simple contrasts of the 6- and 12-week intervention means. Overall comparisons between groups for the outcome measure across follow-up visits were obtained using a contrast to compare average effects across follow-up visits. For aim 3, correlations between serum markers of myogenesis and measures of physical function were analyzed using Spearman’s rank correlation coefficients for non-parametric data and Pearson correlation coefficients for parametric data.

Table 3-1. Inclusion and exclusion criteria

Inclusion Criteria

- Males or females age 60 years and older
- Radiographic evidence of osteophytes
- Pain classification > Grade 0 on Graded Chronic Pain Scale Bilateral standing anterior-posterior radiograph demonstrating Kellgren and Lawrence grade > 1 of the target knee
- Physical limitations evidenced by either:
- Score ≤ 10 on the Short Physical Performance Battery OR
- Walking speed < 1.2 m/sec during or inability to complete 400 m usual-paced test
- Willingness to participate in all study procedures

Exclusion criteria

- Failure to provide informed consent
- Regular participation in progressive, lower-body resistance exercise training within the past 3 months
- Current involvement in supervised rehabilitation program
- Absolute contraindication(s) to exercise training according to American College of Sports Medicine guidelines
- Diagnosed peripheral vascular disease
- Ankle-brachial index < 0.95
- Resting office SBP > 160 mm Hg or < 90 mm Hg
- DBP > 100 mm Hg
- Complicated hypertension indicated by active use of > 2 antihypertensive medications
- Severe cardiac disease, including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest or stroke, use of a cardiac defibrillator, or uncontrolled angina;
- History of Deep venous thrombosis
- Known peripheral neuropathy
- History of rheumatoid arthritis
- Lower limb amputation
- Residence in a nursing home; (persons living in assisted or independent housing will not be excluded)
- Significant cognitive impairment, defined as a known diagnosis of dementia or a Mini-Mental State Examination exam score < 24
- Inability to communicate because of severe hearing loss or speech disorder
- Severe visual impairment, which would preclude completion of the assessments and/or intervention
- Other significant co-morbid disease that would impair ability to participate in the exercise intervention
- Residence outside of the study site or is planning to move out of the area during the study timeframe
- Simultaneous participation in another intervention trial

Table 3-2. Data collection summary by study visit

| Study Phase | Pre-randomization | | Randomization | |
|---|---|---|---|---|
| Visit description (FU=follow-up, CO=close-out) | Screen | Baseline | FU | CO |
| Visit number | 1 | 2 | 3 | 4 |
| Visit week | -2 | 0 | 6 | 12 |
| Informed consent, review inclusion/exlusion criteria | x | | | |
| Personal interview, medical history, MSSE | x | | | |
| Monitor vital signs | x | x | x | x |
| Physical exam | x | | | |
| 400 m walk | x | | x | x |
| SPPB | x | | | x |
| Randomization | | x | | |
| Late-Life Disability Questionnaire | | x | | x |
| Blood collection (CBC, chemical chemistries) | | x | x | x |
| Muscle function | | x | x | x |
| GAITRite® | | x | x | x |

# CHAPTER 4
# RESULTS

## Demographic Characteristics

Participant characteristics are presented in Table 4-1. Briefly, the mean age of the sample was 67.8 ± 5.6 years, 62% of the sample was female, and the mean BMI was 29.7 ± 5.0 $kg*m^{-2}$. The mean 400m walking speed was 1.01 ± 0.13 m/s and the mean SPPB score was 10.4 ± 1.8. Importantly, baseline VAS pain score was statistically significantly higher in the CNTRL group at baseline (28.5 ± 17.9 mm CNTRL vs. 13.8 ±17.5 mm BFR, p=0.02). No other statistically significant differences were observed between groups at baseline.

## Intervention Adherence and Perceived Exertion

Overall attendance to the intervention was 74.1 ± 2.7% for CNTRL vs. 70.0 ± 3.1% for BFR (p=0.691). Overall RPE for the 12-week intervention was similar between groups (8.1 ± 0.5 vs 7.3 ± 0.5, p=0.318). When comparing across sets, overall RPE was higher for the CNTRL intervention (Figure 4-1). However, RPE increased significantly from set one to set three in the BFR group (time*condition interactions for each exercise $p<0.05$, Figure 4-1). To assess perceptual changes over the course of the intervention, overall RPE was calculated for each month of the intervention (i.e. weeks 1-4, weeks 5-8, and weeks 9-12, Figure 4-2). Overall monthly RPE increased significantly in BFR relative to CNTRL over the course of the intervention for leg press ($F(1,21)=14.906$, time*condition interaction p=0.001) and leg extension ($F(1,16)=17.726$, p=0.001), but was similar for leg curl and calf flexion.

## Skeletal Muscle Function

One-repetition maximum testing was performed for each exercise at baseline and week twelve (Table 4-2). Time*condition interactions were not statistically significant for leg press ($F(1,16)=3.44$, $p=0.082$), leg extension ($F(1,12)=4.54$, $p=0.054$), leg curl ($F(1,14)=3.60$, $p=0.078$) or calf flexion ($F(1,16)=0.159$, $p=0.695$). However, increases in leg press (30.3 ± 6.2 kg CNTRL vs. 13.4 ± 6.2 kg BFR), leg extension (17.7 ± 3.9 kg vs. 6.2 ± 3.5 kg) and leg curl (7.8 ± 2.7 kg vs. 0.4 ± 2.7 kg) in response to the intervention tended to favor the CNTRL condition.

Isokinetic knee extensor strength, power and endurance were tested at baseline, week six and week twelve (Figures 4-3 through 4-8). Time*condition interactions revealed no statistically significant differences in knee extensor strength parameters between groups ($p>0.05$). Although not statistically significant, the BFR group demonstrated slightly increased concentric total work at 60 degrees/sec (63.5 ± 32.7 N*m CNTRL vs. 65.2 ± 35.0 N*m BFR, $F(1,23)=0.43$, $p=0.837$), 90 degrees/sec (36.9 ± 24.6 N*m vs. 55.3 ± 26.5 N*m, $F(1,23)=0.25$, $p=0.625$), 120 degrees/sec (24.6 ± 26.4 N*m vs. 26.5 ± 28.5 N*m, $F(1,23)=0.45$, $p=0.835$) and endurance total work (272.2 ± 135.7 N*m vs. 317.8 ± 132.9 N*m, $F(1,21)=0.05$, $p=0.818$) relative to CNTRL. The BFR group also demonstrated a non-statistically significant increase in concentric average power at 90 degrees/sec relative to CNTRL (6.2 ± 4.3 W for CNTRL vs. 11.6 ± 4.6 W for BFR, $F(1,23)=1.293$, $p=0.409$). However, concentric average power tended to favor the CNTRL condition at 60 degrees/sec (11.0 ± 3.5 W CNTRL, 9.1 ± 3.8 W BFR, $F(1,23)=0.226$, $p=0.639$), 120 degrees/sec (9.7 ± 6.5 W CNTRL vs.8.6 ± 7.0 W BFR, $F(1,23)=0.01$, $p=0.912$) and endurance (8.3 ± 3.2 W CNTRL vs. 6.8 ± 3.1 W BFR, $F(1,23)=0.11$, $p=.0744$).

## Measures of Physical Function

Gait speed over 400m was assessed at baseline, week six and week twelve. Change in 400m gait speed was not statistically significantly different between groups, but tended to favor the CNTRL intervention (-0.01 ± 0.03 m/s for CNRL vs. -0.06 ± 0.03 m/s for BFR, group*time interaction $F(1,24)=3.72$, $p=0.065$) (Table 4-3). In contrast, change in gait speed over 4m (0.08 ± 0.02 m/s CNTRL vs. 0.08 ± 0.02 m/s BFR, $F(1,24)=0.01$, $p=0.936$) and change in total balance score (-0.14 ± 0.20 points CNTRL vs. -0.32 ± 0.20 points BFR, $F(1,24)=0.373$, $p=0.547$) were similar between groups in response to the intervention. Finally, total SPPB score tended to increase in both groups at week twelve relative to baseline (0.45 ± 0.35 points CNTRL vs. 0.09 ± 0.35 points BFR, main effect of time $F(1,24)=1.966$, $p=0.174$) but the this change was not statistically significant between groups (time*condition interaction $F(1,24)=0.479$, $p=0.496$).

## Gait

Gait parameters were assessed using the GAITRite® system at baseline, week six and week twelve. Change in average velocity (5.7 ± 2.4 cm/s CNTRL vs. 4.7 ± 2.4 cm/s BFR, time*condition interaction $F(1,23)=0.256$, $p=0.618$) and normalized velocity (0.07 ±0.03 leg lengths/s CNTRL vs.0.05 ±0.03 leg lengths/s $F(1,23)=0.455$, $p=0.507$) were similar between groups in response to the intervention (Figure 4-9). Similarly, changes in the ratio of left to right foot step length were similar between groups (-0.39 ± 0.37 CNTRL vs. -0.01 ± 0.37 BFR, $F(1,23)=0.484$, $p=0.494$) but tended to favor the CNTRL intervention (Figure 4-10). While not statistically significant, changes in single leg stance time tended to favor the BFR group (0.02 ± 0.24% CNTRL vs. 0.30 ± 0.25% BFR, $F( 1,23)=0.576$, p-0.456, Figure 4-11). Finally, changes in toe in/out angle were

similar between groups for the left (F(1,23)=0.266, p=0.611) and right feet (F(1,23)=0.316, p=-.579, Figure 4-12).

### Self-Assessed Pain and Function

Subjective measures of pain and physical function were assessed using the WOMAC and LLFDI questionnaires at baseline and week 12. Changes in WOMAC total score, pain and physical function were similar between groups (all time*interaction p-values >0.05, Table 4-4). While not statistically significant, change in stiffness score tended to favor the BFR group (0.45 ± 0.54 points CNTRL vs. -0.61 ± 0.56 points BFR, F(1,25)=1.536, p=0.227). In contrast, changes in LLFDI tended to favor the CNTRL intervention (Table 4-5). In particular, change in perceived functional limitation total score was significantly higher in CNTRL vs. BFR (11.0 ± 3.3 points CNTRL vs. -5.0 ± 3.0 points BFR, F(1,13)=9.064, p=0.010).

### Body Composition

Body composition was assessed using DEXA at baseline and week twelve (Table 4-6). Change in total mass was similar between groups (-0.39 ± 0.71 kg CNTRL vs. -0.55 ± 0.75 kg BFR, F(1,15)=0.020, p=0.889). However, while not statistically significant, changes in total lean mass (0.36 ± 0.65 kg CNTRL vs. -0.70 ± 0.69 kg BFR, F(1,15)=1.050, p=0.321), fat mass (-1.07 ± -0.56 kg CNTRL vs. 0.37 ± 0.58 kg BFR, F(1,15)=1.808, p=0.199) and body fat percentage (-1.25 ± 0.55% CNTRL vs. 0.37 ± 0.58% BFR, F(1,15)=3.565, p=0.079) tended to favor the CNTRL intervention.

### Serum Measures of Muscle Hypertrophy

Serum IGF-1, TWEAK and P3NP were assessed at baseline, week six and week twelve (Figure 4-13). Change in IGF-1 in response to the intervention was similar between groups (-0.009 ± 0.019 arbitrary units CNTRL vs. -0.011 ± 0.019 units BFR,

F(1,23)=0.189, p=0.878). Serum P3NP expression was significantly reduced from baseline in BFR relative to CNTRL following the intervention (0.03 ± 0.08 units CNTRL vs. -0.23 ± 0.08 units BFR, F(1,23)=5.228, p=0.032). Finally, while not statistically significant, serum TWEAK expression was slightly reduced from baseline in CNTRL relative to BFR following the intervention (-19.0 ± 22.4 pg/mL CNTRL vs. 3.7 ± 20.5 pg/mL BFR, F(1,20)=0.489, p=0.493)

**Correlations**

To determine the relationship between skeletal muscle adaptations and functional outcomes in response the intervention, changes in serum markers of muscle hypertrophy were correlated with study outcomes (Tables 4-7 through 4-15). Serum expression of P3NP, a marker of skeletal muscle collagen synthesis, was demonstrated moderate to strong significant correlations with eccentric isokinetic knee extensor peak torque, power, and work at weeks six and twelve (Tables 4-7 through 4-10). Serum TWEAK was negatively correlated with body fat percentage and total fat mass at baseline and week twelve (Table 4-15).TWEAK also demonstrated a strong, positive correlation with 400m walk speed at baseline and week 12 (Table 4-11).

Table 4-1. Participant characteristics

| | CNTRL N=19 | BFR N=16 | p-value |
|---|---|---|---|
| Age (years) | 69.1±7.1 | 67.2±5.2 | 0.390 |
| Female | 15 (78.9%) | 10 (62.5%) | 0.2833 |
| BMI ($kg*m^{-2}$) | 29.8±5.3 | 31.7±5.9 | 0.327 |
| Minority | 3 (15.8%) | 2 (12.5%) | 0.633 |
| Education | | | 0.102 |
| High school or equivalent | 2 (10.5%) | 2 (12.5%) | |
| Technical degree | | 1 (6.3%) | |
| Some college | 6 (31.6%) | | |
| College degree | 4 (21.1%) | 7 (43.8%) | |
| Professional or grad degree | 6 (31.6%) | 6 (37.5%) | |
| MMSE score | 28.2±1.3 | 28.3±1.5 | 0.831 |
| VAS pain score (mm) | 28.5±17.9 | 13.8±17.5 | 0.020* |
| WOMAC pain | 33.6±19.0 | 30.6±13.7 | 0.597 |
| Daily moderate activity time (3.0-6.0 METs) | 56.1±64.2 | 32.6±22.9 | 0.210 |
| 400m walk speed (m/s) | 1.01±0.11 | 1.04±0.12 | 0.455 |
| SPPB score | 10.2±1.9 | 10.4±1.9 | 0.742 |

All values presented as mean ± standard error or n(%). Abbreviations: BMI=Body mass index. MMSE=Modified mini-mental state examination. VAS=Visual analog scale. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index. MET=metabolic equivalent of task. SPPB=Short physical performance battery.

Table 4-2. One-repetition maximums

| | | CNTRL | | BFR | | |
|---|---|---|---|---|---|---|
| Exercise | Baseline | Wk 12 | Change | Wk 12 | Change | Time*condition (p-value) |
| Leg press | 67.5 ± 0 | 97.8 ± 6.2 | 30.3 ± 6.2 | 80.8 ± 6.2 | 13.4 ± 6.2 | 0.082 |
| Leg extension | 45.4 ± 0 | 63.1 ± 1.0 | 17.7 ± 4.0 | 51.6 ± 1.1 | 6.2 ± 3.5 | 0.054 |
| Leg curl | 45.9 ± 0 | 53.7 ± 10.3 | 7.8 ± 2.7 | 46.3 ± 11.6 | 0.4 ± 2.7 | 0.078 |
| Calf flexion | 72.6 ± 0 | 102.5 ± 4.7 | 29.9 ± 7.6 | 98.1 ± 5.3 | 25.5 ± 7.6 | 0.090 |

Values are expressed in kg and expressed as mean ± standard error. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable.

Table 4-3. Objective measures of physical function

| | | CNTRL | | BFR | | |
|---|---|---|---|---|---|---|
| Variable | Baseline | Wk 12 | Change | Wk 12 | Change | Time*condition (p-value) |
| 400m walk speed (m/s) | 1.05 ± 0 | 1.05 ± 0.01 | -0.01 ± 0.02 | 0.99 ± 0.02 | -0.06 ± 0.02 | 0.065 |
| SPPB gait speed (m/s) | 0.93 ± 0 | 1.02 ± 0.02 | 0.08 ± 0.02 | 1.01 ± 0.02 | 0.08 ± 0.02 | 0.936 |
| Chair stand score | 2.9 ± 0 | 3.3 ± 0.2 | 0.4 ± 0.2 | 3.2 ± 0.2 | 0.3 ± 0.2 | 0.809 |
| Total balance score | 3.8 ± 0 | 3.7 ± 2.0 | -0.1 ± 0.2 | 3.5 ± 0.2 | -0.3 ± 0.2 | 0.547 |
| Total SPPB score | 10.5 ± 0 | 10.9 ± 0.3 | 0.4 ± 0.3 | 10.6 ± 0.3 | 0.1 ± 0.3 | 0.496 |

Values are expressed as mean ± standard error. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable. Abbreviations: SPPB=Short physical performance battery.

Table 4-4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

| | | CNTRL | | BFR | | |
|---|---|---|---|---|---|---|
| Variable | Baseline | Week 12 | Change | Week 12 | Change | Time*condition p-value |
| Total score | 31.9 ± 0 | 29.9 ± 3.3 | -2.0 ± 3.3 | 28.9 ± 3.5 | -3.0 ± 3.5 | 0.850 |
| Pain | 6.9 ± 0 | 5.8 ± 0.9 | -1.1 ± 0.9 | 6.4 ± 0.9 | -0.5 ± 0.9 | 0.673 |
| Stiffness | 3.6 ± 0 | 4.0 ± 0.5 | 0.5 ± 0.5 | 3.0 ± 0.6 | -0.6 ± 0.6 | 0.227 |
| Function | 21.3 ± 0 | 20.1 ± 2.2 | -1.2 ± 2.2 | 18.4 ± 2.3 | -2.9 ± 2.3 | 0.632 |

Values are expressed as mean ± standard error. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable.

Table 4-5. Late Life Function and Disability Instrument

| | | CNTRL | | BFR | | |
|---|---|---|---|---|---|---|
| Variable | Baseline | Week 12 | Change | Week 12 | Change | Time*condition p-value |
| Frequency total scale | 53.0 ± 0 | 54.9 ± 1.6 | 1.9 ± 1.6 | 50.6 ± 1.5 | -2.5 ± 1.5 | 0.111 |
| Frequency social scale | 48.8 ± 0 | 51.1 ± 2.0 | 2.3 ± 2.0 | 45.4 ± 2.0 | -3.4 ± 1.9 | 0.111 |
| Frequency personal scale | 63.9 ± 0 | 68.1 ± 5.4 | 4.2 ± 5.4 | 70.0 ± 5.0 | -2.9 ± 5.0 | 0.430 |
| Limitation total scale | 68.8 ± 0 | 79.8 ± 3.3 | 11.0 ± 3.3 | 63.8 ± 3.0 | -5.0 ± 3.0 | 0.010* |
| Limitation instrumental scale | 68.4 ± 0 | 80.8 ± 4.0 | 12.4 ± 4.0 | 63.7 ± 3.7 | -4.7 ± 3.7 | 0.022* |
| Limitation management scale | 82.8 ± 0 | 92.7 ± 4.5 | 9.9 ± 4.5 | 77.4 ± 4.2 | -5.4 ± 4.2 | 0.055 |

Values are expressed as mean ± standard error. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable. *indicates statistical significance at $p<0.05$.

Table 4-6. Body composition

| | | CNTRL | | BFR | | |
|---|---|---|---|---|---|---|
| Variable | Baseline | Wk 12 | Change | Wk 12 | Change | Time*condition (p-value) |
| Total mass (kg) | 82.4 ± 0 | 82.0 ± 0.7 | -0.4 ± 0.7 | 81.8 ± 0.8 | -0.5 ± 0.8 | 0.889 |
| Total lean mass (kg) | 47.1 ± 0 | 47.4 ± 0.6 | 0.4 ± 0.6 | 46.4 ± 0.7 | -0.7 ± 0.7 | 0.321 |
| Lean mass BMC (kg) | 49.3 ± 0 | 49.8 ± 0.6 | 0.6 ± 0.6 | 48.7 ± 0.6 | -0.5 ± 0.6 | 0.235 |
| Fat mass (kg) | 33.1 ± 0 | 32.1 ± 0.6 | -1.1 ± 0.6 | 33.2 ± 0.6 | 0.1 ± 0.6 | 0.199 |
| Body fat (%) | 40.0 ± 0 | 38.8 ± 0.5 | -1.2 ± 0.5 | 40.4 ± 0.6 | 0.4 ± 0.6 | 0.079 |
| Android/gynoid ratio | 1.06 ± 0 | 1.05 ± 0.02 | -0.01 ± 0.02 | 1.06 ± 0.02 | -0.01 ± 0.02 | 0.847 |

Values are expressed as mean ± standard error. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable. Abbreviations: BMC=Bone mineral content.

Table 4-7. Correlations between serum markers of skeletal muscle hypertrophy and isokinetic knee extensor strength at 60 degrees/s

| | BL | | | 6wk | | | 12wk | |
|---|---|---|---|---|---|---|---|---|
| | IGF1 | P3NP | TWEAK | IGF1 | P3NP | Tweak | IGF1 | P3NP | TWEAK |
| Variable | | | | | | | | | |
| Avg. PT-extension | 0.139 | 0.038 | 0.174 | 0.022 | 0.293 | 0.163 | 0.037 | 0.218 | -0.013 |
| Avg. PT-flexion | 0.058 | 0.214 | 0.214 | -0.089 | 0.517* | 0.151 | -0.194 | 0.482* | 0.037 |
| Avg power-extension | 0.102 | 0.034 | 0.146 | 0.065 | 0.296 | 0.034 | 0.057 | -0.022 | -0.086 |
| Avg. power-flexion | 0.069 | 0.123 | 0.172 | -0.148 | 0.534* | 0.040 | -0.212 | 0.410* | -0.066 |
| Total work-extension | 0.139 | 0.028 | 0.143 | 0.114 | 0.242 | 0.155 | -0.022 | 0.193 | 0.016 |
| Total work-flexion | 0.075 | 0.143 | 0.193 | -0.092 | 0.537* | 0.110 | -0.224 | 0.468* | 0.035 |

Values presented as Pearson correlation coefficient (r). *Indicates statistical significance ($p<0.05$). Abbreviations: PT=Peak torque. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-8. Correlations between serum markers of skeletal muscle hypertrophy and isokinetic knee extensor strength at 90 degrees/s

| | BL | | | 6wk | | | 12wk | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | IGF1 | P3NP | TWEAK | IGF1 | P3NP | Tweak | IGF1 | P3NP | TWEAK |
| Avg. PT-extension | 0.161 | -0.029 | 0.057 | 0.060 | 0.263 | 0.214 | -0.112 | 0.040 | -0.158 |
| Avg. PT-flexion | 0.096 | 0.125 | 0.136 | -0.209 | 0.503* | 0.115 | -0.247 | 0.429* | -0.032 |
| Avg power-extension | 0.102 | 0.034 | 0.146 | 0.065 | 0.296 | 0.034 | 0.057 | -0.022 | -0.086 |
| Avg. power-flexion | 0.069 | 0.123 | 0.172 | -0.148 | 0.534* | 0.040 | -0.212 | 0.410* | -0.066 |
| Total work-extension | 0.193 | -0.043 | 0.069 | 0.129 | 0.201 | 0.160 | -0.083 | 0.012 | -0.111 |
| Total work-flexion | 0.069 | 0.084 | 0.172 | -0.138 | 0.511* | 0.075 | -0.231 | 0.386* | -0.032 |

Values presented as Pearson correlation coefficient (r). *Indicates statistical significance ($p<0.05$). Abbreviations: PT=Peak torque. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-9. Correlations between serum markers of skeletal muscle hypertrophy and isokinetic knee extensor strength at 120degrees/s

| | BL | | | 6wk | | | 12wk | |
|---|---|---|---|---|---|---|---|---|
| | IGF1 | P3NP | Tweak | IGF1 | P3NP | TWEAK | IGF1 | P3NP | TWEAK |
| Variable | | | | | | | | | |
| Avg. PT-extension | 0.202 | -0.121 | -0.003 | 0.118 | 0.059 | -0.014 | 0.076 | 0.010 | -0.013 |
| Avg. PT-flexion | 0.138 | -0.009 | 0.103 | -0.020 | 0.248 | -0.029 | -0.121 | 0.411* | 0.069 |
| Avg power-extension | 0.193 | 0.012 | 0.031 | 0.105 | 0.199 | 0.082 | -0.062 | 0.153 | -0.209 |
| Avg. power-flexion | 0.141 | 0.058 | 0.131 | -0.151 | 0.348 | 0.003 | -0.005 | 0.424* | -0.018 |
| Total work-extension | 0.145 | 0.025 | 0.147 | -0.051 | 0.325 | -0.029 | -0.109 | 0.402* | 0.006 |
| Total work-flexion | 0.193 | -0.044 | 0.019 | 0.212 | 0.121 | 0.095 | -0.027 | 0.111 | -0.080 |

Values presented as Pearson correlation coefficient (r). *Indicates statistical significance ($p<0.05$). Abbreviations: PT=Peak torque. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-10. Correlations between serum markers of skeletal muscle hypertrophy and isokinetic knee extensor endurance

| | BL | | | 6wk | | | 12wk | |
|---|---|---|---|---|---|---|---|---|
| | IGF1 | P3NP | TWEAK | IGF1 | P3NP | Tweak | IGF1 | P3NP | TWEAK |
| Variable | | | | | | | | | |
| Avg. PT-extension | -0.004 | -0.106 | 0.028 | -0.007 | 0.353 | 0.305 | -0.171 | 0.209 | 0.042 |
| Avg. PT-flexion | 0.096 | 0.044 | 0.249 | -0.031 | 0.316 | 0.409* | -0.126 | 0.457* | 0.128 |
| Avg power-extension | -0.030 | -0.066 | -0.010 | -0.022 | 0.352 | 0.257 | -0.151 | 0.240 | 0.024 |
| Avg. power-flexion | 0.019 | 0.150 | 0.162 | -0.114 | 0.340 | 0.247 | -0.111 | 0.437* | 0.112 |
| Total work-extension | -0.045 | -0.057 | 0.000 | 0.112 | 0.210 | 0.258 | -0.066 | 0.141 | 0.055 |
| Total work-flexion | 0.023 | 0.144 | 0.186 | -0.071 | 0.302 | 0.303 | -0.077 | 0.453* | 0.178 |

Values presented as Pearson correlation coefficient (r). *Indicates statistical significance ($p<0.05$). Abbreviations: PT=Peak torque. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-11. Correlations between serum markers of skeletal muscle hypertrophy, 400m walk and SPPB

| | BL | | | 12wk | | |
|---|---|---|---|---|---|---|
| | IGF1 | P3NP | TWEAK | IGF1 | P3NP | TWEAK |
| Variable | | | | | | |
| Fastest walk time | -0.004 | -0.125 | -0.213 | 0.076 | -0.063 | 0.186 |
| Chair stand time | 0.179 | -0.070 | -0.263 | 0.137 | -0.139 | 0.318 |
| SPPB Gait speed | 0.003 | 0.145 | 0.294 | -0.119 | 0.105 | -0.149 |
| 400m walk speed | 0.281 | -0.104 | **0.**561* | 0.243 | -0.040 | 0.508* |
| Total Balance score | 0.106 | -0.008 | 0.066 | -0.103 | 0.042 | -0.008 |
| Speed score | 0.104 | -0.137 | 0.255 | 0.068 | -0.054 | -0.068 |
| Chair score | -0.107 | 0.032 | 0.201 | -0.141 | 0.028 | 0.013 |
| Total score | 0.004 | -0.036 | 0.249 | -0.099 | -0.017 | 0.057 |

Values presented as Pearson correlation coefficient (r). *indicates statistical significance ($p<0.05$). Abbreviations: SPPB=Short physical performance battery. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-12. Correlations between serum markers of skeletal muscle hypertrophy and GAITRite® parameters

| | BL | | | 6wk | | | 12wk | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | IGF1 | P3NP | TWEAK | IGF1 | P3NP | Tweak | IGF1 | P3NP | TWEAK |
| Velocity | 0.159 | -0.008 | 0.060 | -0.006 | 0.039 | -0.097 | 0.096 | 0.014 | -0.133 |
| Normalized velocity | 0.159 | -0.008 | 0.060 | -0.006 | 0.039 | -0.097 | 0.145 | -0.239 | -0.151 |
| Step length differential | 0.106 | -0.176 | 0.085 | 0.211 | -0.048 | 0.149 | 0.063 | -0.008 | 0.189 |
| Cycle time differential | -0.084 | 0.114 | 0.502* | -0.291 | -0.060 | 0.150 | -0.166 | -0.039 | 0.195 |
| Toe in/out right foot | 0.048 | -0.025 | -0.219 | -0.175 | -0.185 | -0.178 | -0.015 | -0.229 | -0.170 |
| Toe in/out left foot | 0.065 | 0.071 | 0.264 | -0.108 | -0.050 | 0.267 | -0.066 | -0.150 | 0.280 |
| Single-leg support | -0.054 | 0.113 | 0.272 | -0.047 | 0.086 | 0.210 | -0.007 | 0.190 | 0.252 |

*Indicates statistical significance ($p<0.05$). Abbreviations: IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-13. Correlations between serum markers of skeletal muscle hypertrophy and WOMAC

| | BL | | | 12wk | | |
|---|---|---|---|---|---|---|
| Variable | IGF1 | P3NP | TWEAK | IGF1 | P3NP | TWEAK |
| Pain | 0.092 | 0.135 | 0.020 | -0.052 | -0.016 | -0.059 |
| Stiffness | 0.035 | 0.081 | -0.091 | 0.190 | 0.163 | -0.270 |
| Physical function | 0.125 | 0.018 | -0.168 | 0.211 | 0.195 | -0.012 |
| Total | 0.104 | 0.045 | -0.149 | 0.044 | 0.096 | 0.010 |

*Values presented as Spearman's rank correlation coefficient (rho). *indicates statistical significance ($p<0.05$). Abbreviations: WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-14. Correlations between serum markers of skeletal muscle hypertrophy and LLFDI

| | BL | | | 12wk | | |
|---|---|---|---|---|---|---|
| | IGF1 | P3NP | TWEAK | IGF1 | P3NP | TWEAK |
| Variable | | | | | | |
| Frequency total | -0.074 | 0.033 | 0.319 | 0.039 | -0.011 | 0.259 |
| Frequency social | 0.159 | 0.006 | 0.321 | -0.355 | 0.013 | 0.417 |
| Frequency personal | -0.184 | 0.085 | 0.270 | -0.171 | 0.035 | 0.301 |
| Limitation total | -0.130 | -0.118 | 0.123 | 0.009 | 0.040 | -0.164 |
| Limitation instrumental | -0.192 | -0.126 | -0.035 | -0.008 | 0.051 | -0.184 |
| Limitation management | 0.143 | -0.096 | 0.292 | 0.118 | -0.051 | -0.282 |

*Values presented as Pearson correlation coefficient (r). LLFDI=Late Life Function and Disability Instrument. IGF1=Insulin-like growth factor-1. P3NP= N-terminal peptide of procollagen type III. TWEAK=Tumor necrosis-like weak inducer of apoptosis

Table 4-15. Correlations between serum markers of skeletal muscle hypertrophy and body composition

| | BL | | | 12wk | | |
|---|---|---|---|---|---|---|
| Variable | IGF1 | P3NP | TWEAK | IGF1 | P3NP | TWEAK |
| Body fat % | 0.030 | 0.087 | -0.392* | 0.183 | -0.257 | -0.417 |
| Android/gynoid ratio | 0.267 | -0.178 | -0.186 | -0.270 | -0.180 | -0.180 |
| Appendicular lean mass/height | 0.136 | -0.257 | -0.094 | -0.136 | -0.018 | 0.145 |
| Total fat mass | 0.087 | 0.005 | -0.457* | -0.028 | -0.236 | -0.489* |
| Total lean mass + BMC | 0.094 | -0.134 | 0.092 | -0.388 | 0.118 | 0.075 |

*Values presented as Pearson correlation coefficient (r). *indicates statistical significance ($p<0.05$).

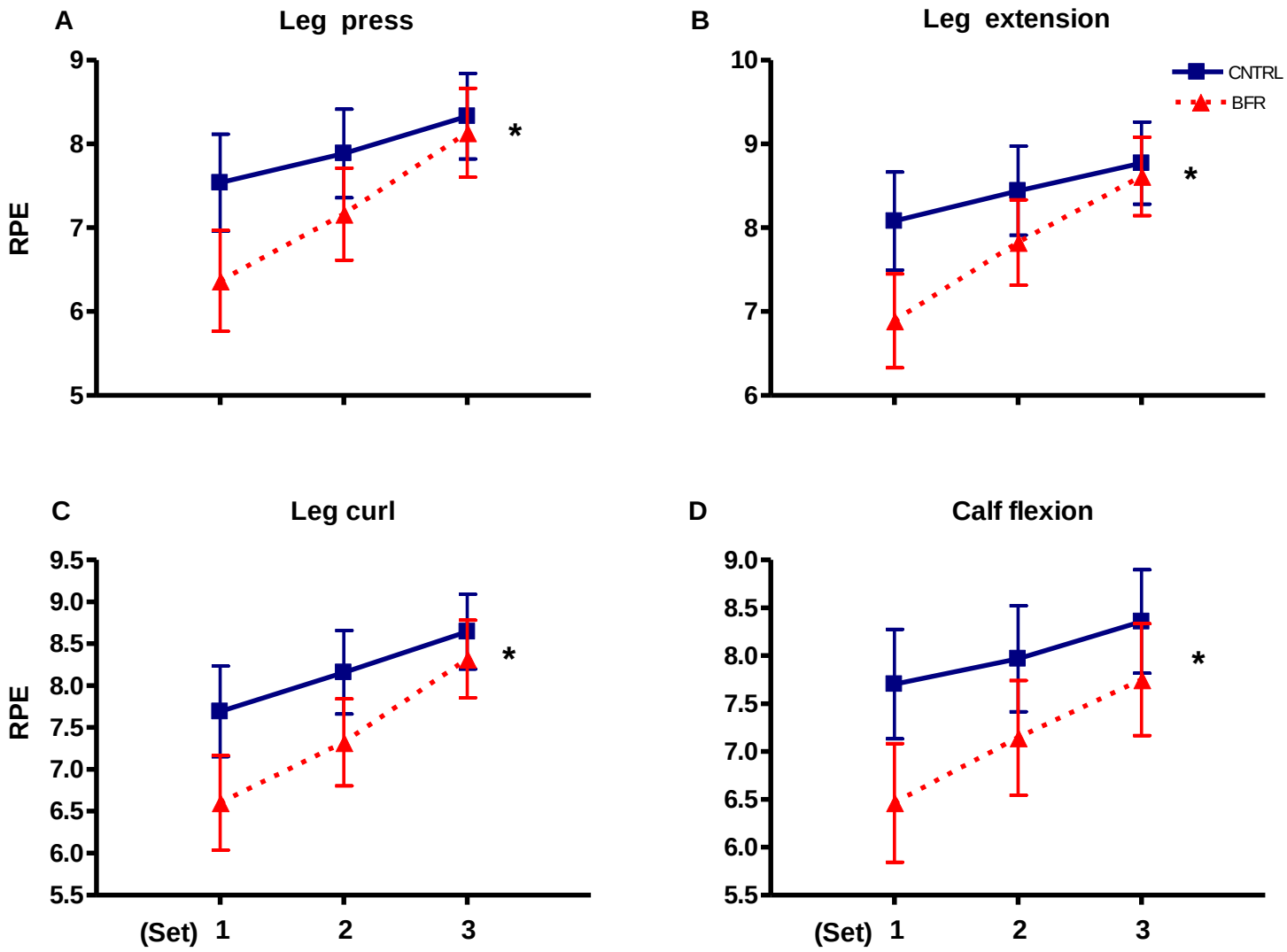


Figure 4-1. Change in ratings of perceived exertion (RPE) across sets for A) leg press B) leg extension C) leg curl D) calf flexion exercises. Model was adjusted for age, sex, baseline pain rating

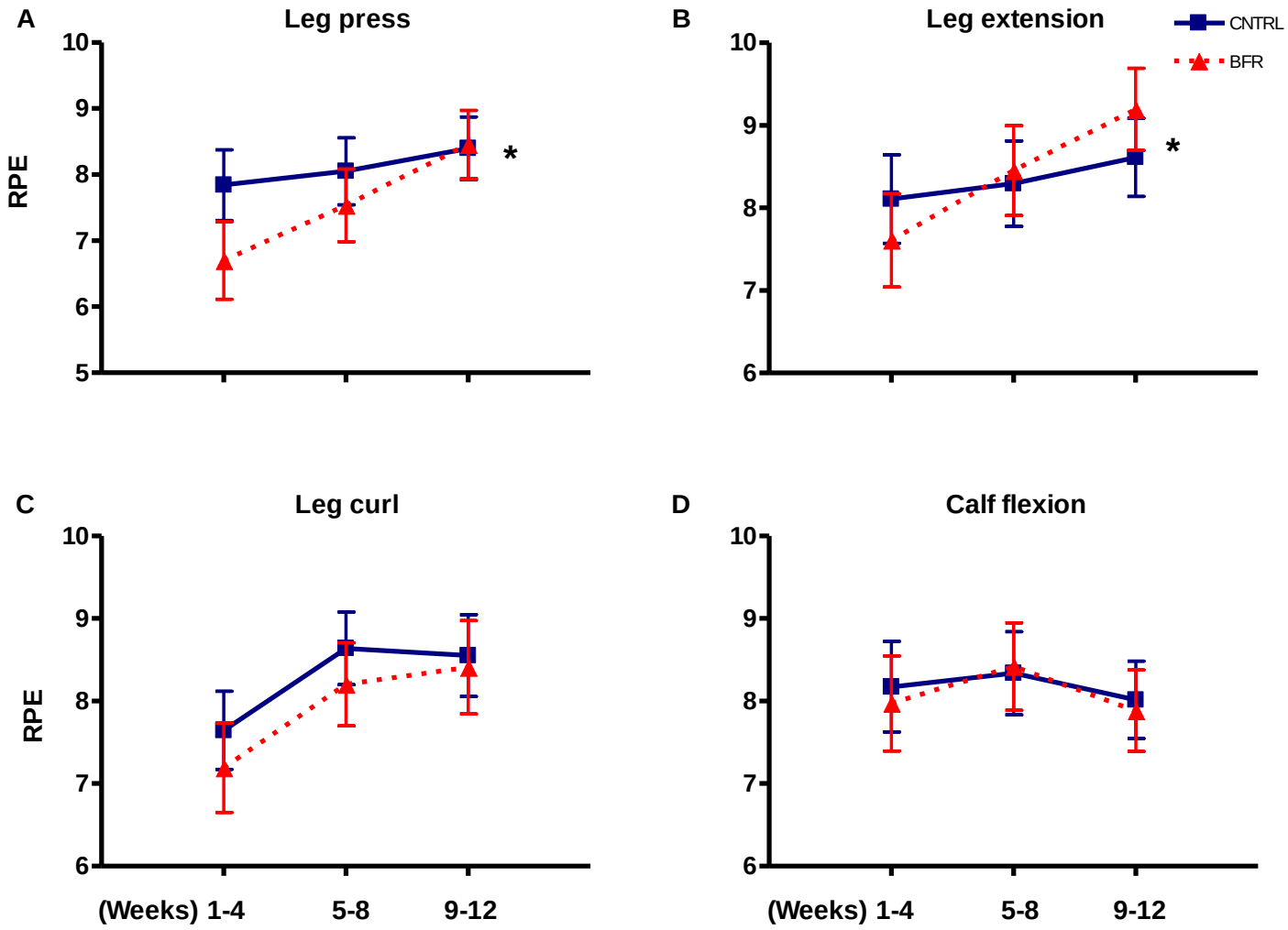


Figure 4-2. Change in ratings of perceived exertion (RPE) across weeks 1-4, 5-8, and 9-12 of the intervention for A) leg press B) leg extension C) leg curl and D) calf flexion exercises. Model was adjusted for age, sex, and baseline pain rating

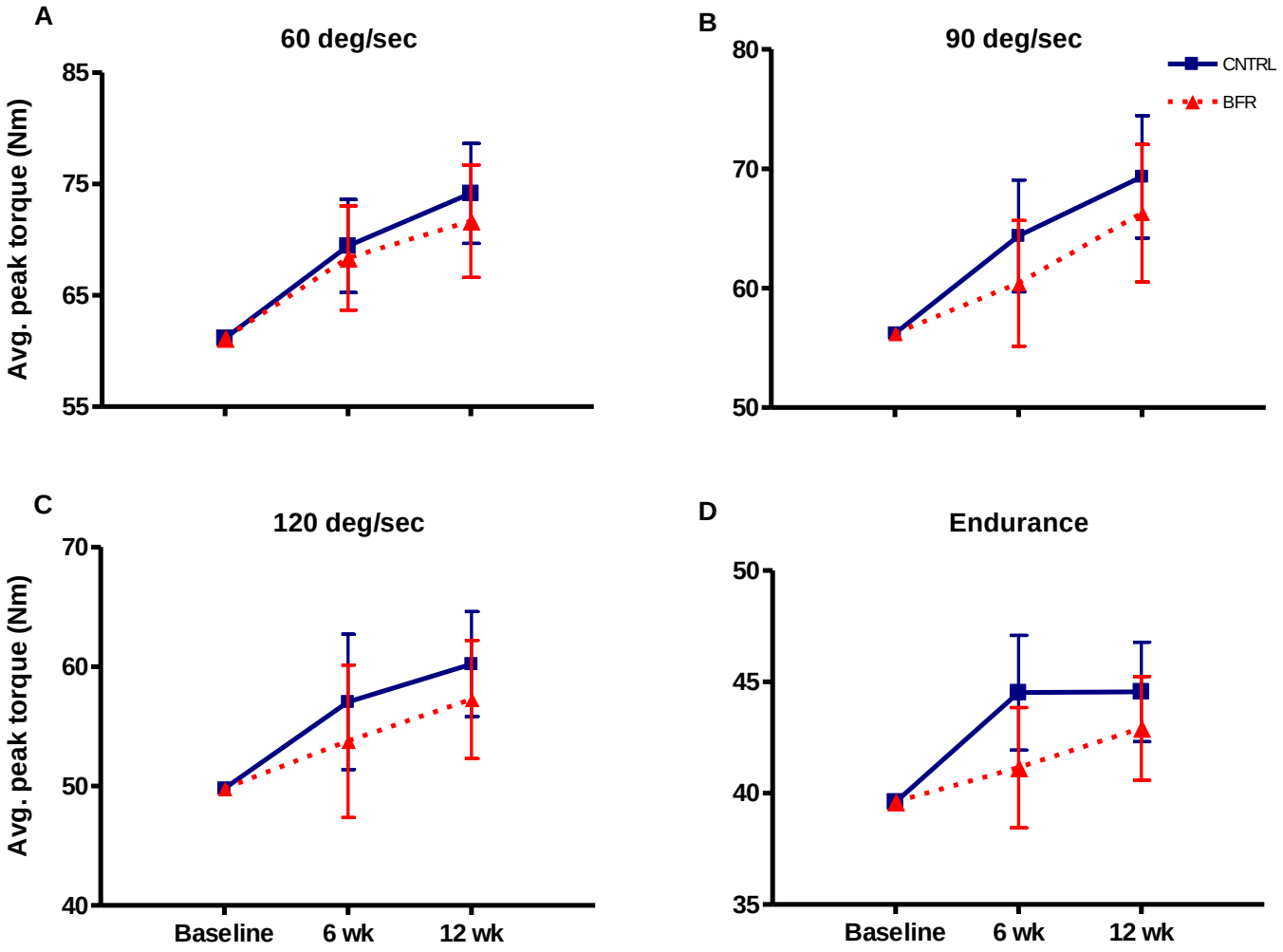


Figure 4-3. Concentric isokinetic knee extensor average peak torque (Newton*meters) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

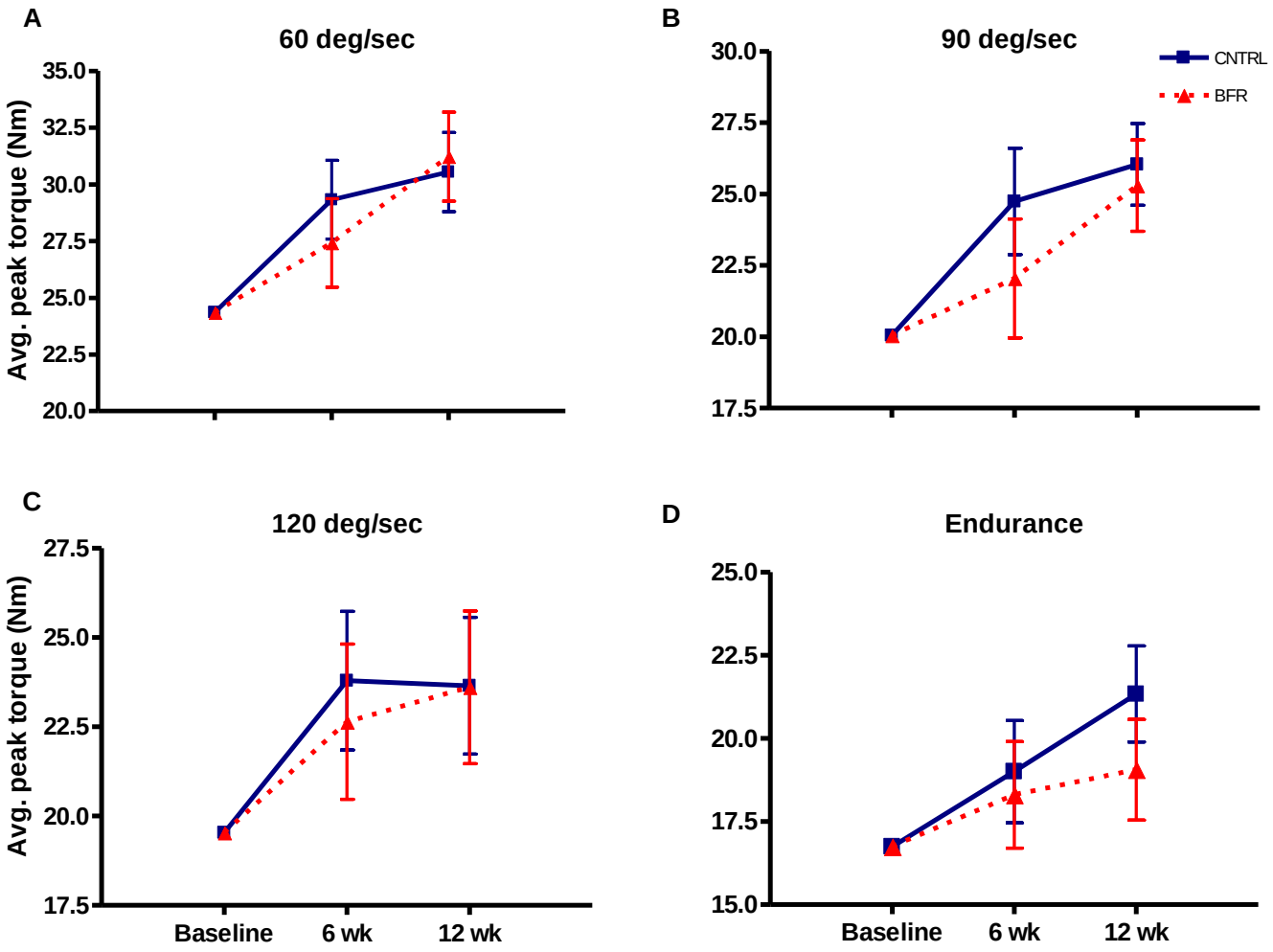


Figure 4-4. Eccentric isokinetic knee extensor average peak torque (Newton*meters) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

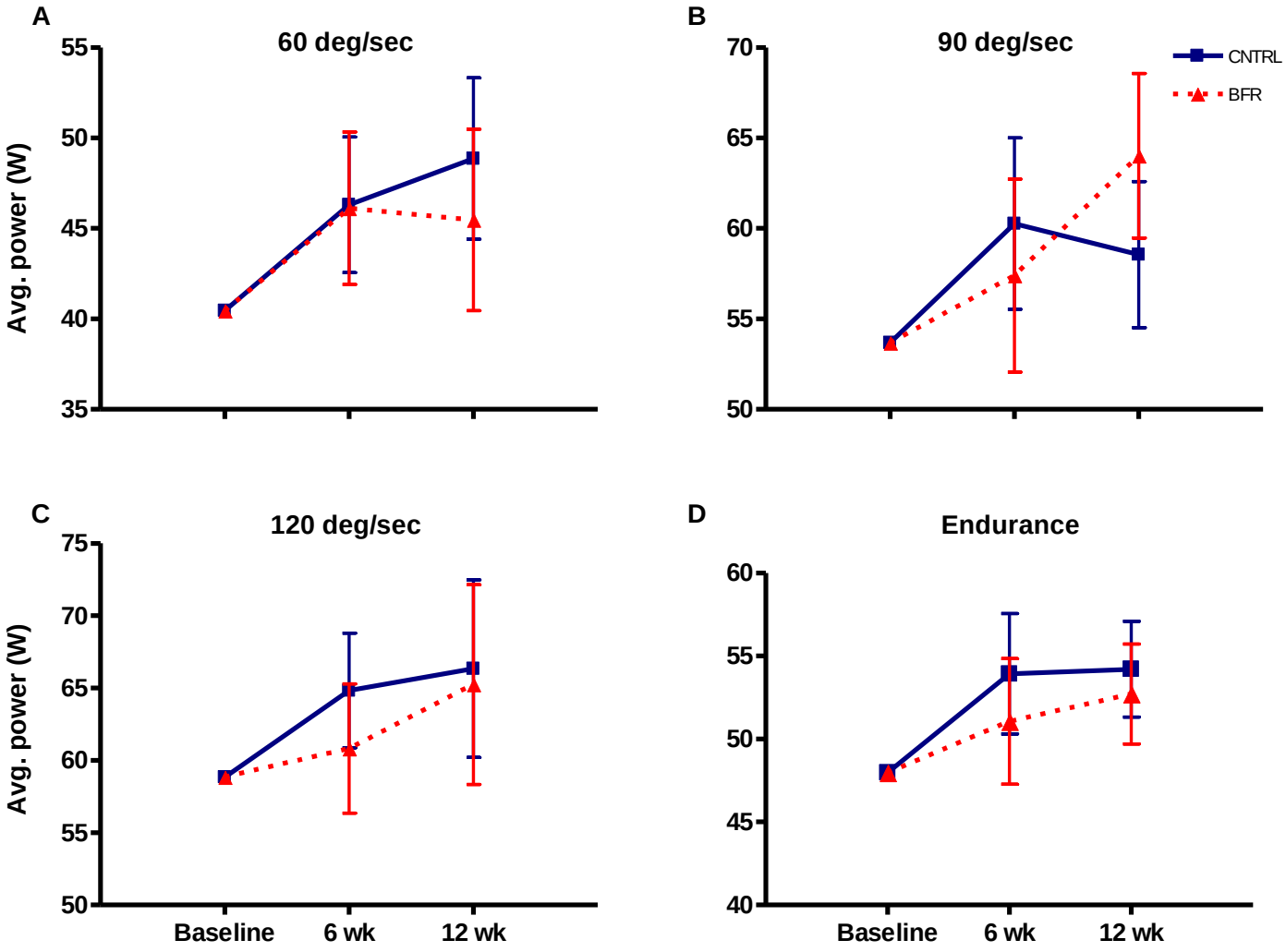


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Figure 4-5. Concentric isokinetic knee extensor average peak power (Watts) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

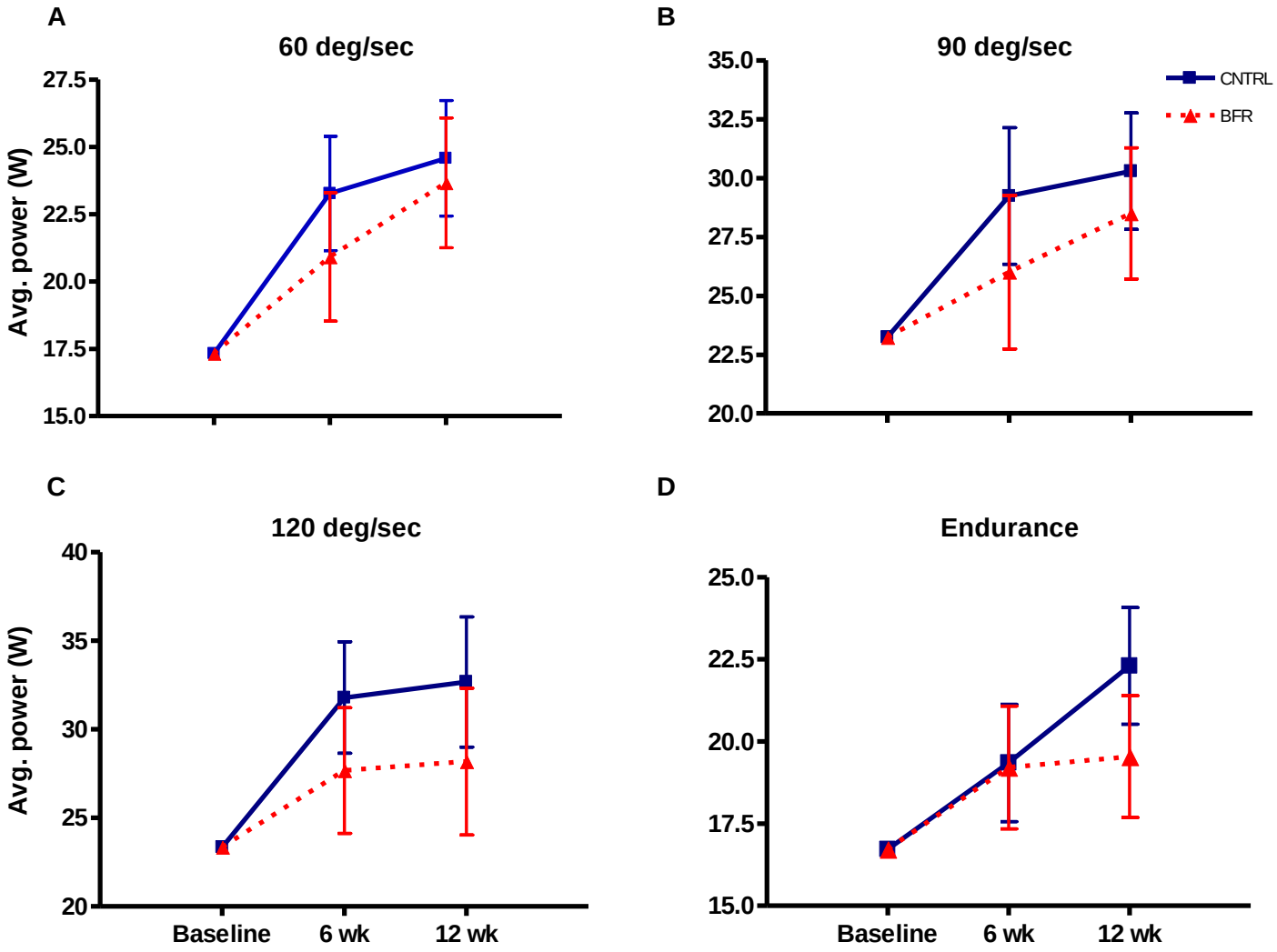


Figure 4-6. Eccentric isokinetic knee extensor average peak power (Watts) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

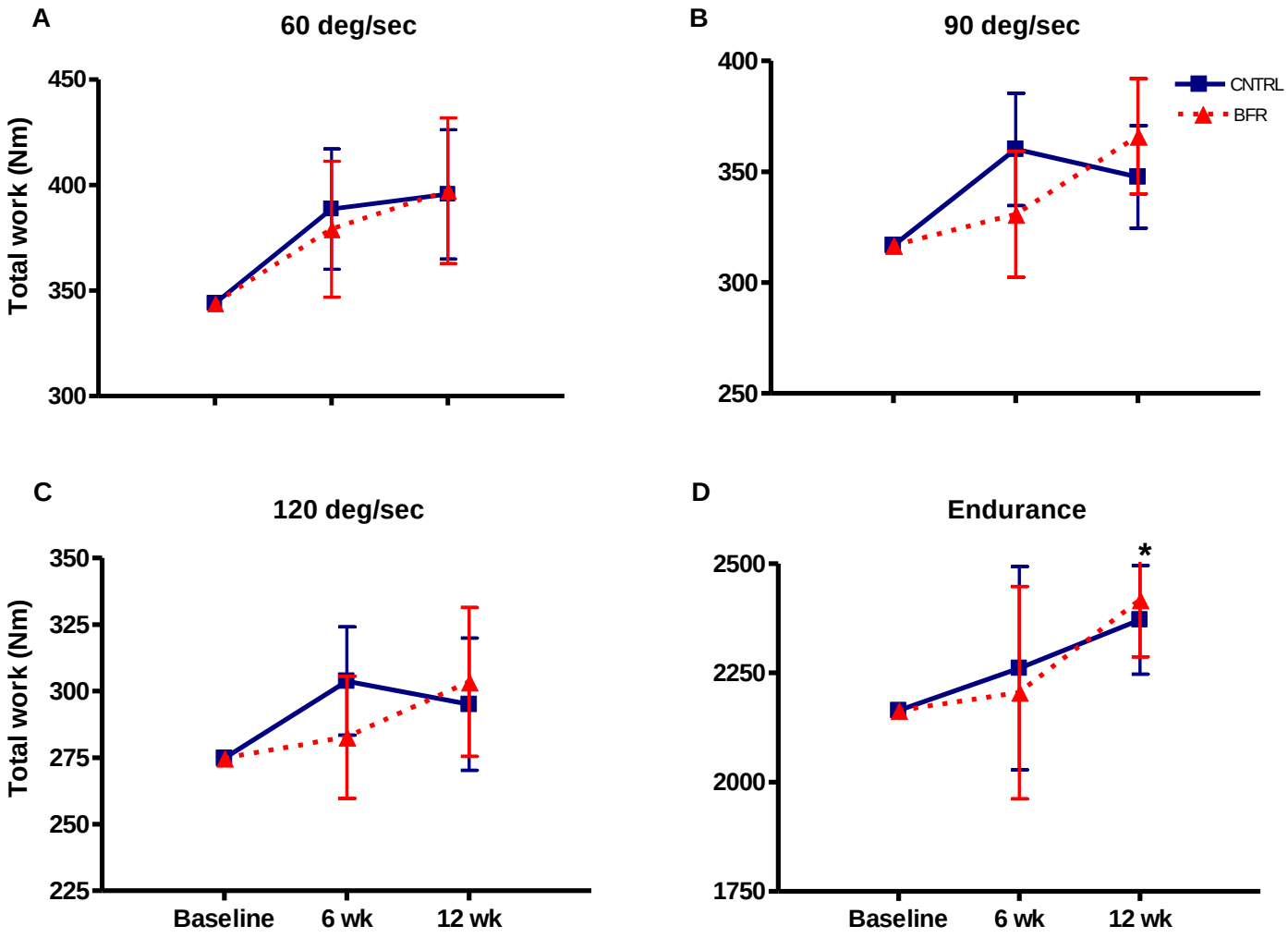


Figure 4-7. Concentric isokinetic knee extensor total work (Newton*meters) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

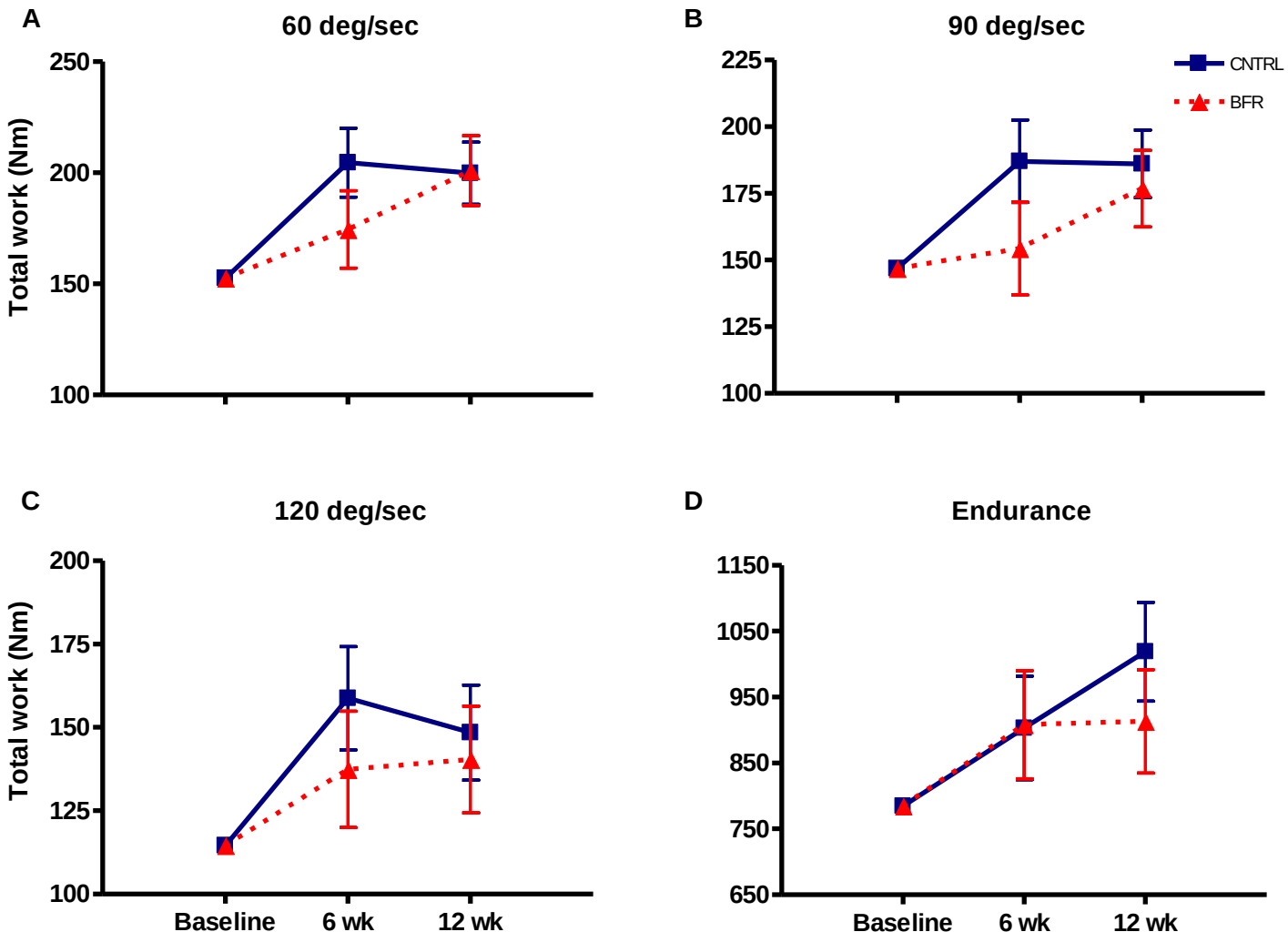


Figure 4-8. Eccentric isokinetic knee extensor total work (Newton*meters) measured at A) 60 degrees/s B) 90 degrees/s C) 120 degrees/s and D) across 50 repetitions (endurance) at 120 degrees/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

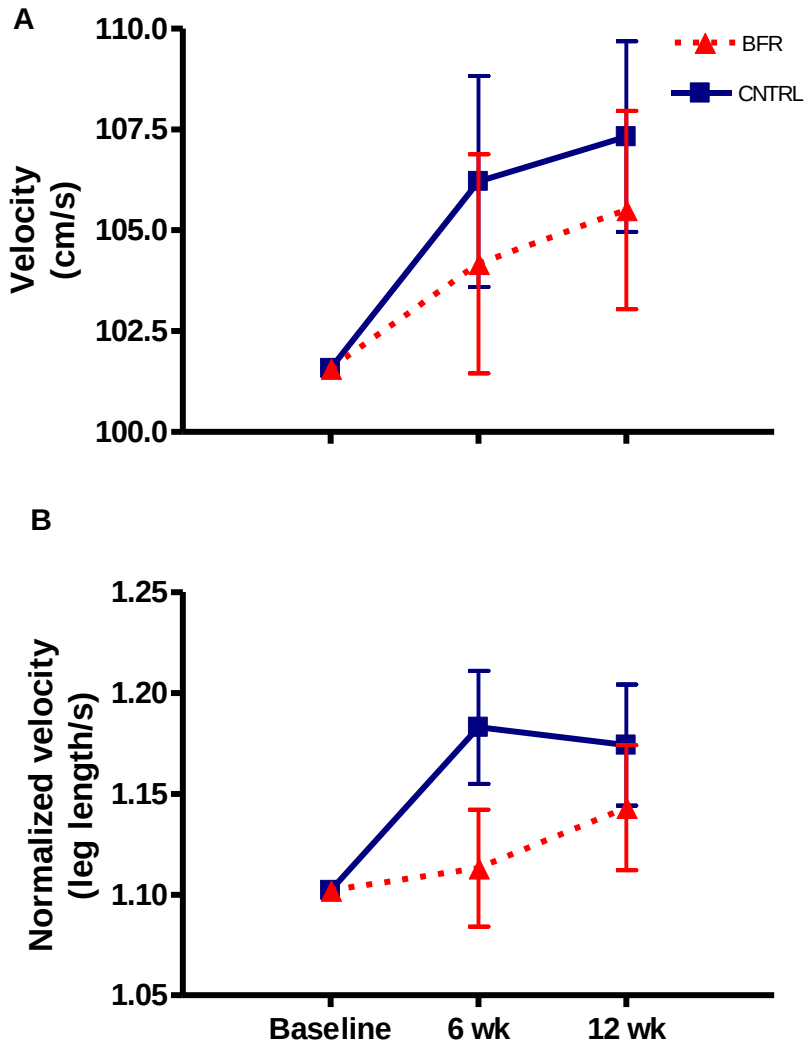


Figure 4-9. Change in gait parameters assessed by GAITRite®. A) Velocity measured in meters/s B) Velocity normalized to leg length and expressed as leg length/s. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

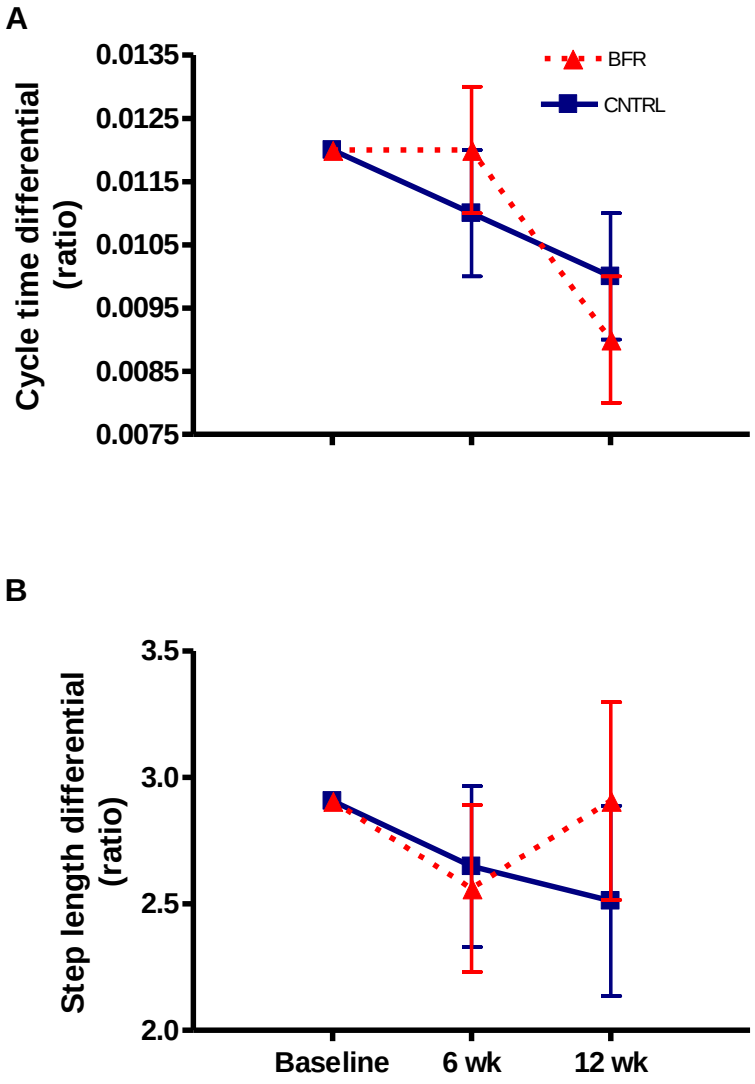


Figure 4-10. Change in gait parameters assessed by GAITRite®. A) Cycle time differential expressed as the ratio of left:right foot cycle time. B) Step length differential expressed as the ratio of left:right foot step length. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

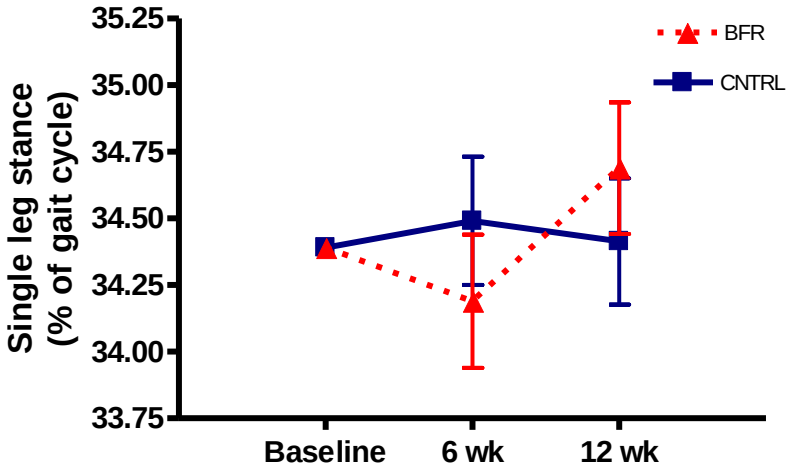


Figure 4-11. Change in gait parameters assessed by GAITRite®. A) Cycle time differential expressed as the ratio of left:right foot cycle time. B) Step length differential express as the ratio of left:right foot step length. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

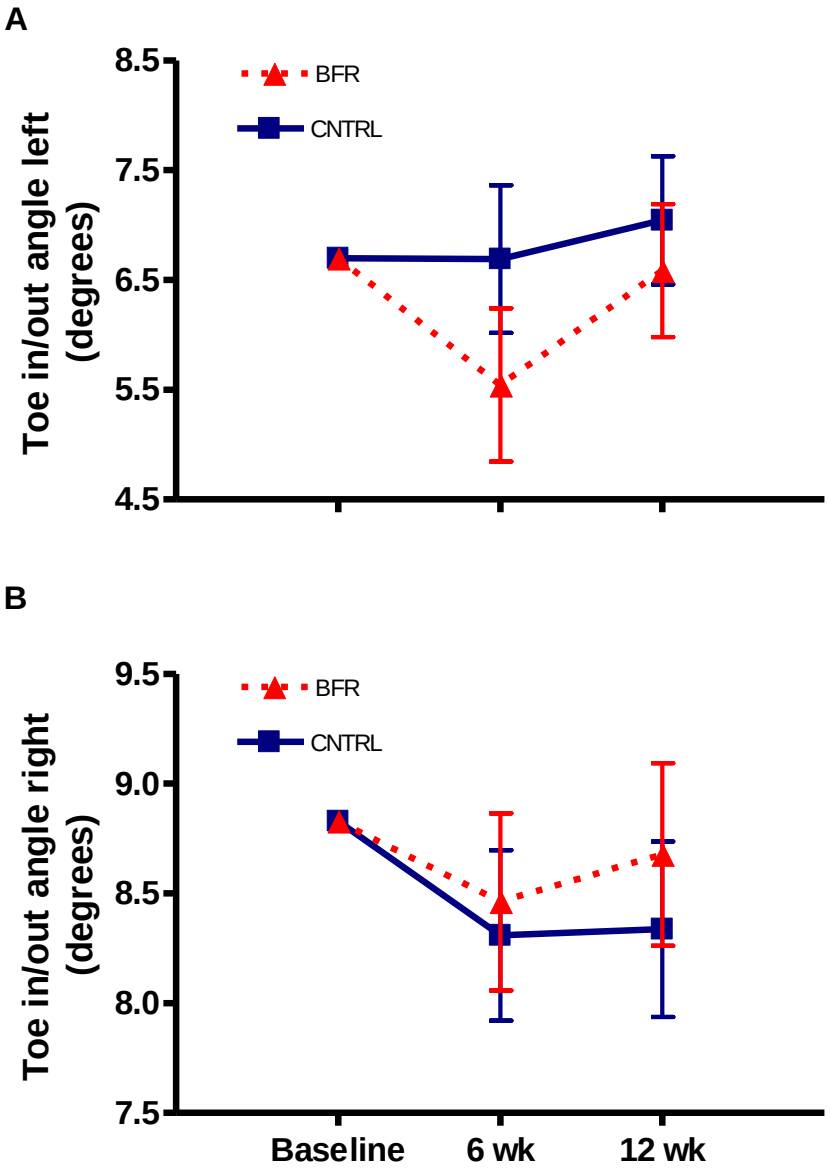


Figure 4-12. Change in gait parameters assessed by GAITRite®. A) Toe in/out angle of left the left foot expressed as degrees of deviation from midline B) Toe in/out angle of left the right foot expressed as degrees of deviation from midline. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

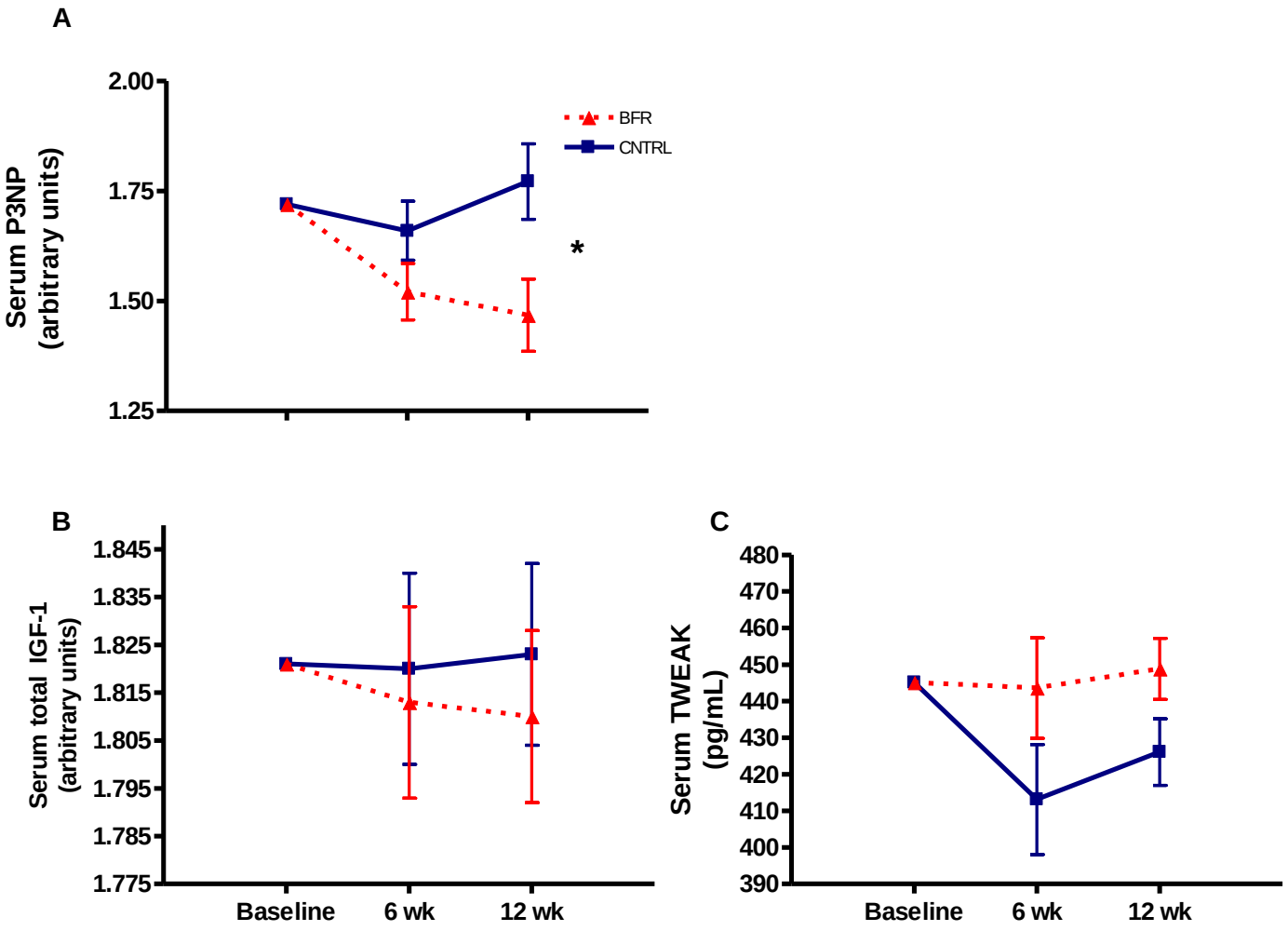


Figure 4-13. Change in serum markers of skeletal muscle hypertrophy. A) Serum N-terminal peptide of procollagen type III (P3NP) B) Serum insulin-like growth factor-1. C) Serum tumor necrosis-like weak inducer of apoptosis. Model was adjusted for age, sex, baseline pain rating and baseline value of the corresponding variable

# CHAPTER 5
# DISCUSSION

The primary objective of the present analysis was to assess the physical and skeletal muscle functional adaptations to twelve weeks of lower-body resistance exercise alone or combined with BFR among older adults with knee OA. Secondarily, we assessed changes in serum markers of skeletal muscle hypertrophy and determined their relationship to changes in muscle function, body composition and physical function. The primary findings from the present analysis indicate that changes in lower body strength assessed by 1RM and isokinetic knee extensor strength parameters tended to favor the CNTRL group. Furthermore, 400m walk speed, subjective measures of physical function (LLFDI) and changes in body composition (body fat mass, lean mass) also tended to favor the CNTRL group. Other measures including objective measures of physical function (SPPB), subjective measures of pain (WOMAC) and gait parameters were similar between groups. Additionally, serum P3NP expression was significantly higher in CNTRL compared to BFR at week 12, while serum total IGF-1 tended to be higher in CNTRL. Serum TWEAK tended to be lower in CNTRL at week 12. Finally, we found that serum P3NP was positively associated with eccentric isokinetic knee extensor strength parameters, while serum TWEAK demonstrated a strong, positive association with 400m walk speed and a moderate, negative association with body fat mass.

The addition of BFR to low-load resistance exercise was previously shown to increase skeletal muscle strength relative to low-load exercise alone.[5] However, the majority of studies in healthy adults report greater increased strength from traditional high-load exercise compared to BFR.[5,159] Our findings indicate that strength changes

were not statistically significantly different between BFR and CNTRL. However, the majority of isokinetic knee extensor strength measures and changes in 1RMs tended to favor CNTRL over BFR. To our knowledge, only one other study has compared BFR to high-load exercise in persons with knee OA. In contrast to the present study, Bryk et al.[133] reported greater isometric knee extensor strength gains in BFR (30% 1RM, 200mmHg cuff pressure) relative to high-load training (70% 1RM). However, some key differences between these studies may explain this discrepancy. For example, the training protocol utilized by Bryk et al. was similar between groups with the exception of seated knee extensions which were performed with or without BFR. These additional exercises (e.g. hip and thigh adduction abduction) performed with similar loads may have augmented the BFR training response. Furthermore, the BFR group used a higher load for training (30% vs 20% in the present study). Finally, Bryk et al. prescribed a set number of repetitions as opposed to performing exercises to volitional fatigue.[204] More research is needed to determine optimal training variables to elicit knee extensor strength adaptations, as knee extensor strength is associated with risk of symptomatic knee OA,[160] pain,[31,40] joint space narrowing[161-163] , cartilage thickness[43,49,164] and physical function[165] in persons with OA.

Additionally, the knee extensors play an important role in shock absorption and gait stability during ambulation.[46,47,166] As a result, knee extensor weakness may lead to altered gait mechanics,[44,45] which can increase OA risk or accelerate joint damage.[167] Specifically, the knee extensors are activated eccentrically during the contact phase of the gait cycle and prevent forward excursion of the knee,[168] such that persons with greater ability to produce eccentric force have less knee damage over time.[169]

Furthermore, knee extensor eccentric force is associated with knee pain, function[170] and balance in persons with OA.[171] Although these associations were not explored in the present analysis, several objective (gait speed) and subjective measures of physical function (LLFDI) tended to favor the CNTRL intervention. Although speculative, these findings may be at least partially explained by the tendency to increase knee extensor eccentric force characteristics in the CNTRL group relative to BFR.

Interestingly, we found moderate to strong correlations between P3NP--a serum marker of skeletal muscle hypertrophy produced during skeletal muscle collagen formation[14]--and knee extensor eccentric peak torque, power, and total work. This finding suggests that the relative increase in knee extensor eccentric force production may be due to increased skeletal muscle hypertrophy. In support of this hypothesis, we found that the CNTRL group tended to increase lean body mass relative to BFR over the course of the intervention. However, this remains speculative as we did not directly measure changes in knee extensor skeletal muscle CSA or thigh mass. Furthermore, it is unclear why P3NP expression is correlated only with eccentric knee extensor force characteristics. While speculative, it is likely that the lower load used for the BFR intervention was not a sufficient stimulus to evoke optimal adaptations for eccentric force production. For example, Yasuda et al.[172] compared eccentric-only BFR exercise to concentric-eccentric BFR exercise. The concentric-eccentric training evoked significant increases in skeletal muscle CSA and strength, while these measures were unchanged after eccentric-only exercise. These findings may warrant future research, as knee extensor eccentric strength is a major determinant of physical function in persons with knee OA.[173]

Although changes in strength tended to favor the CNTRL intervention, it is also important to consider the perceptual responses to the interventions as higher perceived exertion may result in lower adherence over time. Previous studies have shown higher-load training may have lower adherence rates than lighter load training in persons with OA.[80] In the present analysis, overall RPE was significantly lower in BFR relative to CNTRL. This is consistent with numerous BFR studies showing that RPE is lower for BFR compared to high-load training.[174-177] However, RPE increased significantly across sets (set 1 to set 3) and over time (month 1 to month 3) relative to CNTRL. This finding is in contrast to a longitudinal study showing that RPE significantly decreases with subsequent training sessions with BFR (20% 1RM) relative to high-load training (85% 1RM).[174] However, this study was performed in recreationally active young males which may partially explain this discrepancy. Nonetheless, our findings indicate that while BFR appears to be better-tolerated overall relative to high-load training, there are marked perceptual changes over time that could potentially limit the long-term applicability of BFR training in older adults with knee OA.

Despite this potential limitation, BFR may be particularly appropriate as a short-term intervention for improving strength in lower functioning patients or patients awaiting joint replacement. Furthermore, RPE in BFR training can be impacted by numerous factors including cuff size and material,[178,179] occlusion pressure,[180] type of pressure application (i.e. continuous vs. intermittent),[176] load,[174] and exercise modality. Thus clinicians looking to implement BFR training long-term for persons with musculoskeletal disorders may consider varying these factors to offset changes in perceptual responses with training. However, more work is needed to confirm the validity of this approach.

Persons with OA are at significantly greater risk of becoming disabled. [21,22] Thus assessment of physical function is critical for determining the efficacy of interventions in older adults with knee OA. Functional tests such as the SPPB and 400m walk have been validated among older adults for testing physical function and are highly associated with disability risk and mortality.[145,154,181] In the present analysis, while not statistically significant, 400m walk speed tended to decrease in BFR. Furthermore, this decrease was clinically significant (-0.05 m/s).[182] In contrast, gait speed over 4m tended to increase to a similar extent in both groups following the intervention. It is unclear what caused this discrepancy, as related knee extensor strength parameters[183-185] including peak torque, power, and peak torque to body mass (not shown) tended to increase over the course of the intervention in both groups. However, it should be noted that while both the 4m and 400m walk tests are measures of lower-extremity function, the 400m walk test is likely influenced by aerobic fitness and capacity and therefore may be more sensitive to factors that affect endurance (e.g. cardiovascular comorbidities or sarcopenic obesity[186]).

In support of this hypothesis, the BFR group tended to increase fat mass and lose lean mass over the course of the intervention, whereas the CNTRL group tended to lose fat mass and gain lean mass. Although knee extensor peak torque relative to body weight tended to increase in the BFR group (not shown), these changes in body composition may have negatively impacted the endurance capabilities of participants in the BFR group, resulting in lower gait speed over 400m. Interestingly, we also found that serum TWEAK demonstrated a strong, positive correlation with 400m gait speed both at baseline and at 12 weeks. While acute increases in TWEAK signaling following

exercise are associated with skeletal muscle myogenesis through alternative NFκB signaling, [187] chronically elevated TWEAK expression is associated with skeletal muscle atrophy, [188,189] cardiovascular morbidities[190] and obesity.[191] However, we found that serum TWEAK demonstrated a moderate, negative correlation with total fat mass and body fat percentage at baseline and week 12. These correlations and changes in body composition and function correspond with a trend toward a decrease in serum TWEAK in CNTRL versus no change in BFR. Although we cannot establish a causal relationship between changes in serum TWEAK and these outcomes, these findings indicate that persons with higher serum TWEAK have lower body fat mass and higher gait speed over 400m. However, as this relationship is in contrast to much of the published literature, extensive follow up will be needed to confirm this association and determine the efficacy of serum TWEAK as a biomarker of physical function in persons with OA.

In addition to slower walking speed and reduced physical function, persons with knee OA tend to have altered gait parameters relative to healthy controls.[192] These alterations appear to become more pronounced with increasing disease severity.[167] For example, persons with OA have greater step length and cycle time differential, which are indicative of gait asymmetry. In turn, gait asymmetry is associated with physical function, fall risk[193,194] and joint degradation[195] on older adults. In the present study, cycle time differential tended to decrease in both groups, while step length differential only tended to decrease in the CNTRL group at week 12. While step length differential was decreased at week 6 in BFR, it returned to baseline levels at week 12. Although the reason for this reversal is unclear, it may be important to follow-up with future studies to determine the role of strength training for improving gait asymmetry in persons with OA.

To our knowledge, no study to date has explored this relationship. However, Laroche et al.[196] observed greater gait asymmetry in persons with knee extensor strength asymmetry between legs. Thus, targeting strength asymmetry with resistance exercise may be a potential preventative or rehabilitative intervention for persons with knee OA.

Another gait abnormality associated with knee osteoarthritis is the toe in/out angle. Specifically, greater toe-out angle reduces knee adduction moment (KAM) in the coronal plane during ambulation.[197] However, it has been suggested that patients with knee OA are unable to toe-out effectively due to knee and shank misalignment.[197] Greater toe-out angle is associated with lower symptomatic OA[198] and a reduced risk of OA disease progression, likely due to reduction of KAM and other loading forces on the knee during gait.[199] In the present study, toe-out angle tended to decrease at week 6 in the BFR group (left foot), but returned to baseline at week 12. In contrast, toe-out angle tended to increase slightly in the CNTRL group. Toe-out angle tended to decrease to a similar extent in both groups for the right foot. To our knowledge, the impact of resistance training on toe-out angle has not been explored in the literature. However, increases in toe-out angle were observed in persons recovering from knee arthroplasty, and this increase corresponded with recovery of knee and hip musculature strength.[200] Furthermore, targeted gait interventions have demonstrated that toe-out angle can be adapted.[198] Future studies may explore the use strength training to augment targeted gait training for increasing toe-out angle in persons with knee OA.

We also evaluated changes in single leg stance (SLS) in response to the intervention. This gait parameter measures the percentage of the gait cycle spent supported on one leg (i.e. while the opposite leg swings forward). Persons with OA have

smaller SLS relative to healthy controls,[201] and this appears to be a compensation strategy to reduce joint loading on the affected side.[19] In healthy adults, SLS is reportedly 38-40%.[202] Participants in our study had slightly lower SLS than healthy adults (34.4% at baseline), which is consistent with a previous study.[203] While SLS did not change over the course of the intervention for the CNTRL group, SLS decreased at week 6 but recovered to near baseline levels at week 12 in the BFR group. While it is unclear why SLS initially decline in the BFR group, this change may be partially explained by changes in pain and self-assessed function.[204] Although we showed a trend toward a decrease in WOMAC stiffness in the BFR group relative to CNTRL, physical limitations on the LLFDI significantly increased in CNTRL relative to BFR, indicating lower function in the BFR group. While speculative, these changes in self-assessed pain and function may partially explain the unfavorable changes in gait speed, step length differential and SLS in BFR observed in the present study.[205] Thus, these associations and their underlying causes may warrant future research. Furthermore, while changes in SLS with resistance exercise have not been explored, patients recovering from hip arthroplasty increased SLS on the affected limb two years after surgery, and this increase corresponded with recovery of knee musculature strength.[18] This suggests that improving muscle strength may improve SLS, possibly by reducing pain and guarding behavior during ambulation.

**Limitations**

The strengths of the present study include a clinically-relevant population and outcomes, good adherence to the exercise interventions, and a relatively long period of intervention and follow-up. However, this trial was designed as a pilot trial to determine

the efficacy and feasibility of BFR training for older adults with knee OA, with the intention of performing a larger, fully powered trial in the future. Thus the present study was not statistically powered to detect differences in study outcomes and results must be interpreted with caution. Another potential limitation is that the participants performed all exercises to volitional fatigue. We chose this method of training to account for differences in workload resulting from the use of a fixed repetition prescription with different loading paradigms between groups. Indeed, performance of resistance exercise to volitional fatigue results in similar strength and skeletal muscle hypertrophic responses between high and low-load exercise.[206,207] However, we cannot rule out that differences in workload may have significantly influenced outcomes such as body composition. Another limitation of the present study involves technical limitations with the C-terminal agrin fragment (CAF) analysis. We had planned to evaluate changes in serum CAF, a serum marker of skeletal muscle hypertrophy and neuromuscular adaptations.[208] However, due to technical problems with the analysis kits this analysis could not be completed. The addition of serum CAF measurements could have helped to clarify the mechanisms linking skeletal muscle adaptations such as hypertrophy with changes in knee extensor strength and other functional outcomes. This objective could have been further augmented by direct measurement of skeletal muscle CSA and related hypertrophy markers (e.g. TWEAK receptor FN14, satellite cell activity, and myogenic regulatory factors) from skeletal muscle tissue. Future studies are needed to evaluate these possibilities.

A final limitation with the present study involves the methods used to induce BFR. As discussed previously, a number of factors may dictate the outcomes to BFR

training, including cuff width and material, occlusion pressure, intermittent vs. continuous pressure application, exercise modality and load (%1RM). At the present time, no optimal combination of these factors has been identified for maximizing skeletal muscle strength and functional outcomes, particularly in persons with knee OA. As a result, caution is advised when comparing the results of this study with other trials utilizing different training protocols. While experimentally difficult, outcomes may be further optimized by introducing variation of these and other factors throughout the intervention. For example, knee extensor power[209] and eccentric strength[210] are important determinants of function and disease progression in persons with knee OA. Thus inclusion of power training and/or eccentric-accentuated exercises may be beneficial for improving knee extensor strength parameters when using BFR training in this population.

## Conclusions

We found that changes in skeletal muscle strength, walking speed, subjective measures of physical function and body composition tended to favor the CNTRL group following twelve weeks of either high-load resistance exercise (CNTRL) or low-load resistance exercise combined with BFR in older adults with knee OA. Other outcomes objective measures of physical function (SPPB) and self-assessed pain and stiffness were similar between groups. Furthermore, we found that serum expression of TWEAK and P3NP were associated with numerous outcomes including eccentric knee extensor strength parameters, walking speed over 400m and changes in body fat mass. Thus, these measures have potential utility as biomarkers of functional changes in response

to exercise interventions. However, results from the present study must be interpreted with caution as the trial was not designed to assess changes in these outcomes.

APPENDIX A
WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX

# WOMAC

Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely. Circle **one number** for each activity.

| | | | | | | |
|---|---|---|---|---|---|---|
| Pain | 1. Walking | 0 | 1 | 2 | 3 | 4 |
| | 2. Stair Climbing | 0 | 1 | 2 | 3 | 4 |
| | 3. Nocturnal | 0 | 1 | 2 | 3 | 4 |
| | 4. Rest | 0 | 1 | 2 | 3 | 4 |
| | 5. Weight bearing | 0 | 1 | 2 | 3 | 4 |
| Stiffness | 1. Morning stiffness | 0 | 1 | 2 | 3 | 4 |
| | 2. Stiffness occurring later in the day | 0 | 1 | 2 | 3 | 4 |
| Physical Function | 1. Descending stairs | 0 | 1 | 2 | 3 | 4 |
| | 2. Ascending stairs | 0 | 1 | 2 | 3 | 4 |
| | 3. Rising from sitting | 0 | 1 | 2 | 3 | 4 |
| | 4. Standing | 0 | 1 | 2 | 3 | 4 |
| | 5. Bending to floor | 0 | 1 | 2 | 3 | 4 |
| | 6. Walking on flat surface | 0 | 1 | 2 | 3 | 4 |
| | 7. Getting in / out of car | 0 | 1 | 2 | 3 | 4 |
| | 8. Going shopping | 0 | 1 | 2 | 3 | 4 |
| | 9. Putting on socks | 0 | 1 | 2 | 3 | 4 |
| | 10. Lying in bed | 0 | 1 | 2 | 3 | 4 |
| | 11.Taking off socks | 0 | 1 | 2 | 3 | 4 |
| | 12. Rising from bed | 0 | 1 | 2 | 3 | 4 |
| | 13. Getting in / out of bath | 0 | 1 | 2 | 3 | 4 |
| | 14. Sitting | 0 | 1 | 2 | 3 | 4 |
| | 15. Getting on / off toilet | 0 | 1 | 2 | 3 | 4 |
| | 16. Heavy domestic duties | 0 | 1 | 2 | 3 | 4 |
| | 17. Light domestic duties | 0 | 1 | 2 | 3 | 4 |

Total score: _____ / 96 = _____%

Com-
ments:_____

APPENDIX B
LATE LIFE FUNCTION AND DISABILITY INSTRUMENT


# Late Life FDI: Disability component


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## Contents

## INSTRUCTIONS FOR DISABILITY QUESTIONS:

In this set of questions, I will ask you about everyday things you do at this time in your life. There are two parts to each question.

First, I will ask you *How often* you do a certain activity.
Next, I will ask you *To what extent do you feel limited* in doing this activity.

**Explain each question and subsequent answer options:**

For the first question (*How often do you do the activity?*), please choose from these answers:

- **Very often**
- **Often**
- **Once in a while**
- **Almost never**
- **Never**

[Show visual aid to interviewee]

For the second question (*To what extent do you feel limited in doing the activity?*), please choose from these answers:

- **Not at all**
- **A little**
- **Somewhat**
- **A lot**
- **Completely**

[Show the visual aid to interviewee]

For example, you might feel limited because of your health, or because it takes a lot of mental and physical energy. Please keep in mind that you can also feel limited by factors outside of yourself. Your environment could restrict you from doing the things; for instance, transportation issues, accessibility, and social or economic circumstances could limit you from doing things you would like to do. Think of all these factors when you answer this section.

For each question, please select the one answer that comes closest to the way you have been feeling.
Let's begin…

## Disability Questions

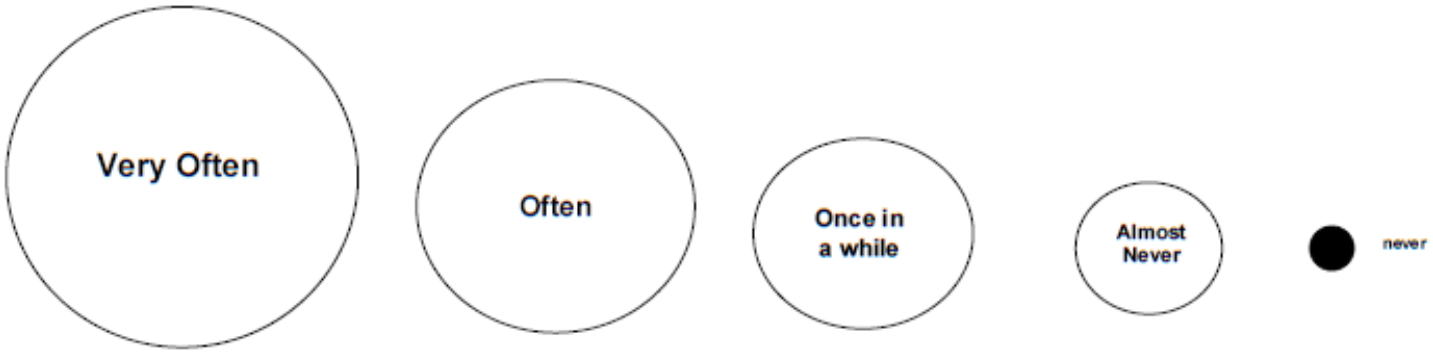
| | How often do you…? | | | | | To what extent do you feel limited in …? | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Very Often | Often | Once in a while | Almost never | Never | Not at all | A little | Somewhat | A lot | Completely |
| **D1. Keep (Keeping) in touch with others through letters, phone, or email.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D2. Visit (Visiting) friends and family in their homes.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D3. Provide (Providing) care or assistance to others. This may include providing personal care, transportation, and running errands for family members or friends.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D4. Take (Taking) care of the inside of your home. This includes managing and taking responsibility for homemaking, laundry, housecleaning and minor household repairs.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D5. Work (Working) at a volunteer job outside your home.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D6. Take (Taking) part in active recreation. This may include bowling, golf, tennis, hiking, jogging, or swimming.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D7. Take (Taking) care of household business and finances. This may include managing and taking responsibility for your money, paying bills, dealing with a landlord or tenants, dealing with utility companies or governmental agencies.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D8. Take (Taking) care of your own health. This may include managing daily medications, following a special diet, scheduling doctor's appointments.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |

## Disability Questions, continued

| | How often do you…? | | | | | To what extent do you feel limited in …? | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Very Often | Often | Once in a While | Almost never | Never | Not at all | A little | Somewhat | A lot | Completely |
| **D9. Travel (Traveling) out of town for at least an overnight stay.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D10. Take (Taking) part in a regular fitness program.** This may include walking for exercise, stationary biking, weight lifting, or exercise classes. | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D11. Invite (Inviting) people into your home for a meal or entertainment.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D12. Go (Going) out with others to public places such as restaurants or movies.** | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D13. Take (Taking) care of your own personal care needs.** This includes bathing, dressing, and toileting. | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D14. Take (Taking) part in organized social activities.** This may include clubs, card playing, senior center events, community or religious groups. | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D15. Take (Taking) care of local errands.** This may include managing and taking responsibility for shopping for food and personal items, and going to the bank, library, or dry cleaner. | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |
| **D16. Prepare (Preparing) meals for yourself.** This includes planning, cooking, serving, and cleaning up. | 5 | 4 | 3 | 2 | 1 | 5 | 4 | 3 | 2 | 1 |

DISABILITY VISUAL AID #1

## How often do you…?




Frequently

A lot of the time

A major part of your life

Regularly

A regular part of your life

Infrequently

From time to time

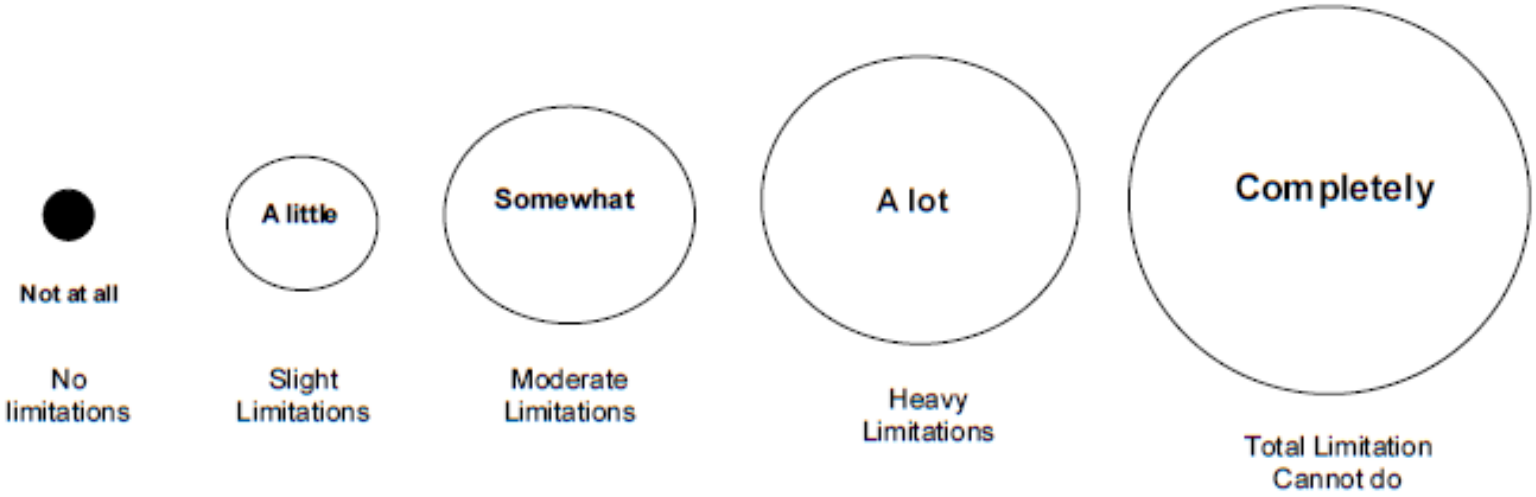
Occasionally

Very infrequently

Rarely

DISABILITY VISUAL AID #2

## To what extent do you feel limited in … ?




Examples of limiting factors that may restrict you:

- Mental or Physical Energy
- Too much effort
- Social and economic circumstances
- Transportation problems
- Accessibility issues
- Health

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# BIOGRAPHICAL SKETCH

Andrew Steven Layne earned a Bachelor of Science degree in exercise science from East Tennessee State University in 2008 and a Master of Arts in exercise physiology in 2010. Andrew then received a graduate school fellowship award to begin his doctoral studies in exercise physiology at the University of Florida, which he completed in 2017. Throughout his training, Andrew's focus has been on improving physical performance through resistance exercise. Andrew has worked with a wide range of populations from athletes to the elderly in research, commercial and corporate settings.