Resistance Training to Improve Energy Metabolism, Body Composition, and Physical Function in Rheumatoid Arthritis

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List of Common terms and Abbreviations

RA – Rheumatoid arthritis

RC – Rheumatoid cachexia

REE - Resting energy expenditure

BMI – Body mass index

FMI – Fat-mass index

FFMI – Fat-free mass index

PRT+FLEX – Progressive resistance training and flexibility

FLEX – Flexibility

Acknowledgments

Jordan Koch told me during a squash game that research is all about the relationships you make. I’m thankful to all the faculty, all my peers, and my Redmen teammates who made my two years at McGill incredible. From my supervisors Ross Andersen and Susan Bartlett, to my lab mates, especially Alex, Ryan, and Pat, to Paul, to 456, 4055, and 3993, thanks for the amazing memories.

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by high levels of inflammation, pain, disability, and pre-mature mortality. RA places a significant burden on individuals and the healthcare system as people with RA are more likely to be disabled. Unfavourable changes in energy metabolism and body composition may contribute substantially to the disability and poor health-related quality of life associated with RA.

The purpose of this project was to conduct a pilot trial exploring the feasibility and safety of a 12-week progressive resistance training program (PRT) on physical function in RA. A secondary objective was to explore potential mechanisms associated with changes in physical function including energy metabolism, body composition, and muscle strength. It was hypothesized that the 12-week program would result in improved physical function, body composition, muscle strength, and energy metabolism. Eighteen participants with RA (17 females, mean (SD) age 38 (19) years, weight of 65.1 (8.4) kg, RA duration of 8 (5) years) were included in this study. All were sedentary, under the care of a rheumatologist and had received clearance to exercise. At baseline, participants provided sociodemographic information and completed validated questionnaires assessing perceived physical function/disability (i.e., PROMIS-4a, MDHAQ, RA-FQ Physical Function). They also completed questionnaires that assessed disease activity (RAPID3 and RA-FQ), exercise self-efficacy, physical activity enjoyment, and daily physical activity. Participants also underwent tests assessing resting energy expenditure assessment (REE), body composition (dual energy x-ray absorptiometry), and physical function tests (Short Performance Physical Battery, 400-m walk, muscle strength). Participants were randomized to 12 weeks of either a resistance training + flexibility PRT+FLEX); or flexibility (FLEX). The PRF+FLEX group completed two supervised workouts

using resistance training equipment and range of motion (FLEX) exercises, and one home-based workout per week using elastic resistance bands. The FLEX group completed the same range of motion (FLEX) exercises at home. Repeated measures ANOVA revealed statistically significant interaction effects in body fat percentage (p = .010), fat-mass index (p = .017), RA-FQ Physical Function (p = .002), RA-FQ disease activity (p = .002), RAPID3 (p = .002), and physical activity enjoyment (p = .026) that favoured the PRT+FLEX over the FLEX group. Additionally, there was an effect of time for appendicular lean mass (p = .028), lower body lean mass (p = .030), PROMIS-4a (p = .002), MDHAQ (p = .005), 400-m walk (p = .002), knee flexion strength (p = .008) and REE (p = .014) with the PRT+FLEX group improving more than the FLEX group. There was no between group differences for total body mass, bone mass, lean mass, SPPB, visceral fat, number of cachectic participants, knee extension strength, exercise self-efficacy, and daily physical activity. The findings of this study suggest that a 12-week resistance exercise program is feasible, safe, and enjoyable in people with RA and can improve physical function, body composition, and muscle strength.

Résumé

L'arthrite rhumatoïde (AR) est une maladie immunitaire chronique caractérisée par des niveaux élevés d'inflammation, de douleur, d'incapacité et de mortalité prématurée. La maladie de l'AR peut être diagnostiquée à n'importe quel moment dans la vie d'un individu et elle constitue un fardeau important pour la société et le système de santé, dû aux nombreuses comorbidités et l'aide quotidienne qu'ont besoin les personnes atteintes par cette maladie. De plus, l'AR est souvent associée à une diminution de la masse musculaire, de la force, du métabolisme énergétique ce qui joue un rôle important sur les fonctions physiques et la qualité de vie des personnes atteintes par cette maladie.

Le but de ce projet était d'examiner les effets d'un programme de musculation de 12 semaines sur les fonctions physiques des personnes atteintes de l'AR. Notre objectif secondaire était d'explorer les changements dans la composition corporelle, la force musculaire et la dépense énergétique au repos à la suite du programme. Dix-huit participants (17 femmes et 1 homme, âge = 38 (19) ans, poids = 65,1 (8,4) kg, durée de la maladie = 8 (5) ans) ont été inclus dans cette étude. Tous les participants avaient un diagnostic médical de l'AR, ils étaient sédentaires depuis au moins trois mois et ils avaient l'autorisation de leur rhumatologue d'exécuter un programme d'entraînement supervisé. Au début, les participants devaient remplir des questionnaires sur leurs propres caractéristiques (éducation, activité de la maladie, médicaments) et sur leur incapacité (p. ex. PROMIS-4A, RA-FQ, MDHAQ), tout en complétant une absorptiométrie à rayons-X à double énergie. Ils devaient également participer aux tests mesurant les fonctions physiques (batterie de courte durée, marche de 400 m), à un test de force musculaire et à une évaluation de la dépense énergétique au repos. Une fois les évaluations de bases complétées, les participants ont été aléatoirement choisis pour participer soit au groupe de

résistance + flexibilité (PRT + FLEX), ou au groupe de flexibilité (FLEX). Le programme d'exercices exigeait que les participants effectuent deux entrainements supervisés (y compris des exercices de flexibilité) et un entrainement à la maison par semaine en utilisant des bandes de résistance élastique tandis que le groupe de flexibilité effectuait des exercices d'amplitude non-supervisés. Des améliorations cliniquement significatives aux examens des fonctions physiques (MDHAQ, PROMIS-Fonction physique 4A) ont été observées pour les deux groupes, cependant, le groupe PRT + FLEX avait de meilleurs résultats que le groupe FLEX dans toutes les évaluations des fonctions physiques. Les mesures répétées ANOVA ont révélé des effets d'interaction statistiquement significatifs au niveau du pourcentage de graisse corporelle ($p = 0,010$), l'indice de masse graisseuse ($p = 0,017$), la fonction physique (RA-FQ) ($p = 0,001$), et le plaisir lié à l'activité physique (p =. 026), ce qui a favorisé le PRT + FLEX comparativement au groupe FLEX. Les résultats de cette étude ont des implications cliniques importantes à cause des améliorations des fonction physique et de la composition corporelle révélées par le programme de musculation de 12 semaines. Pour les professionnels de la santé, cette étude renforce la sécurité et l'efficacité de la prescription d'exercices de musculation aux patients atteints de l'AR afin d'améliorer les fonctions physiques et la composition corporelle. Chaque fois que cela est approprié, un entrainement de résistance devrait être recommandé pour les personnes atteintes de cette importante maladie.

Preface and Authors Contributions

Nathan Chiarlitti and Alexandra Sirois helped design the study, recruited and consented participants, supervised exercise sessions, and collected, analyzed, and interpreted study data.

Dr. Ross E. Andersen, Professor, Department of Kinesiology and Physical Education, and Dr. Susan J. Bartlett, Professor of Medicine, Department of Medicine, McGill University co-supervised these activities and assumed responsibility for all scientific activities and oversight of this thesis.

Chapter 1 – Introduction

1.1 Scope of the Problem

Rheumatoid arthritis (RA) is a painful and debilitating chronic inflammatory disease that is associated with excess morbidity and mortality (Cutolo, Kitas, & van Riel, 2014; Uhlig, Moe, & Kvien, 2014). RA confers a significant burden to individuals, the healthcare system, and society. Compared to healthy individuals, people with RA are two times more limited in daily activities and are 30% more likely to need day-to-day assistance (Ma, Chan, & Carruthers, 2014). RA-related disability is related to altered body composition, reduced physical function, joint deformities, severe fatigue, and poor health-related quality of life (HRQL) (Baker, Von Feldt, et al., 2014; Cooney, Law, Matschke, Lemmey, Moore, Ahmad, Jones, et al., 2011; Giles, Bartlett, Andersen, Fontaine, & Bathon, 2008). HRQL is an individual's perception of their overall health, and encompasses mental, physical and social health (Wilson and Cleary, 1995).

The excess of systemic circulating inflammatory cytokines associated with RA can shift protein metabolism towards a catabolic state and result in significant loss of muscle mass (Rall, Rosen, et al., 1996; Walsmith & Roubenoff, 2002). This shift in body composition is known as rheumatoid cachexia. Rheumatoid cachexia plays a major role in the reduced physical function and impaired health-related quality of life (HRQL) associated with RA as lean tissue mass is directly related to strength and the ability to perform basic activities of daily living.

Pharmacological treatment for RA is directed at suppressing inflammation (Uhlig et al., 2014). Although combinations of RA medications can be effective in reducing disease activity, many of the newer, more effective treatments are also very expensive and contribute to the substantial economic burden associated with RA (Bansback et al., 2017). Recent treatment strategies that emphasize remission (i.e., no detectable disease activity) can improve physical function but may not improve body composition (Lemmey et al., 2016). Further, one randomized controlled study in RA conducted over nearly 2 years found that biologic therapy was associated with increased body fat (Engvall, Tengstrand, Brismar, & Hafström, 2010).

The relationship between body composition changes and increased disability has been well documented in RA (Baker, Østergaard, et al., 2014; Giles et al., 2008; Kramer, Fontaine, Bathon, & Giles, 2012). Resting energy expenditure (REE) is often elevated in people with RA, reflecting a state of hypermetabolism, and in turn, is associated with reduced muscle mass and strength which ultimately impairs physical function. Thus, identifying new treatment strategies that can help normalize energy metabolism, improve body composition, and increase muscle strength and quality have the potential to improve health, physical function, and HRQL in people with RA.

The conceptual framework used for this study is grounded in the theoretical approach developed by Wilson and Cleary (Wilson & Cleary, 1995). The Wilson-Cleary framework links biomedical health and quality of life focusing with patient valued outcomes such as physiology changes, symptoms, physical functioning, health perceptions, and HRQL. Individual and environmental factors also influence each of these factors. Since its creation over 20 years ago, the Wilson and Cleary model has been the most widely used, and cited HRQL conceptual framework (Bakas et al., 2012; Ojelabi, Graham, Haighton, & Ling, 2017). In a recent systematic review, the Wilson and Cleary model was shown to be clear, concise, unique to HRQL, and hypothesis driven, allowing researchers to apply biological factors to everyday life (Bakas et al., 2012). In the adapted model (Figure 1), we show how RA inflammation (change in physiological status) impacts body composition, metabolism (resting energy metabolism), symptom status (muscle strength), and functional status (physical function) which are mediated by both personal and environmental factors.

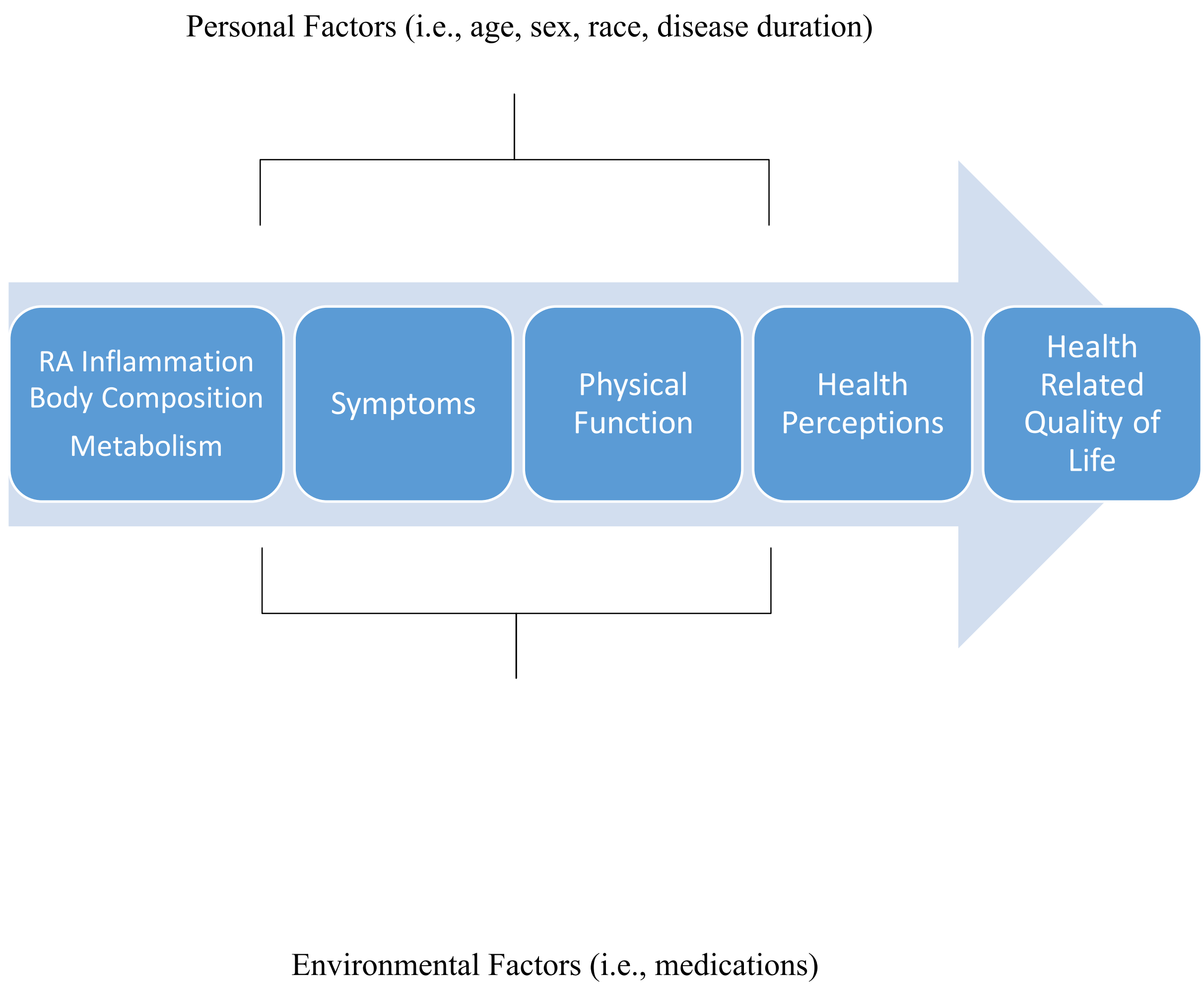

Figure 1. Adaptation of the Wilson-Cleary model showing interrelationships among physiologic changes, symptoms, physical function and health-related quality of life associated with rheumatoid arthritis.

1.2 Rationale

It has been over 20 years since the first resistance training study was conducted in people with RA (Rall, Meydani, Kehayias, Dawson-Hughes, & Roubenoff, 1996). Since then, several small resistance training studies have been shown to be safe and effective at improving health and physical function (Flint-Wagner et al., 2009; Lemmey et al., 2009; Marcora, Lemmey, & Maddison, 2005). However, most studies have been small, varied in the type and length of training program used, and did not use a rigorous study design or outcomes to explore mechanisms that may explain understand mechanisms associated with improved physical function.

For example, only one study has measured change in metabolism in response to exercise (Rall, Meydani, et al., 1996). This study used low training volumes (five exercises, completed twice a week for 12 weeks) compared to later studies (Lemmey et al., 2009; Marcora et al., 2005). Additionally, this study was conducted prior to the use of new therapeutics (i.e., biologics and combinations of medications) and early intensive treatment strategies which can dramatically control inflammation and improve outcomes in RA. Further, no study in RA has combined supervised resistance training with a home-based program to provide sufficient frequency while reducing participant burden. A home component may also promote long-term adherence as typically, once supervised exercises ends, adherence declines (Lemmey, Williams, Marcora, Jones, & Maddison, 2012). Finally, to date, every resistance study has used the same five to eight exercises each workout for the entire duration of the training program. To be safe and effective, exercise programs must be specifically tailored to the needs and preferences of people with RA (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015). Teaching participants to exercise safety and providing new exercises including simple variations adapted to individual needs may increase exercise self-efficacy, exercise enjoyment, and promote long-term adherence (ACSM, 2013).

1.3 Purpose

The primary objective of this randomized controlled pilot study was to evaluate recruitment rate, the safety and acceptability of two exercise programs (resistance training + flexibility training - PRT+FLEX vs. Flexibility - FLEX), and the feasibility of measurement methods and outcomes in preparation for a larger full-scale trial. We also explored the impact of 12 weeks of either PRT+FLEX or FLEX training on physical function and hypothesized mechanisms (i.e., metabolism, body composition, muscle strength) associated with improved physical function.

1.4 Objectives

Objective #1: To compare the effects of a 12-week resistance training + flexibility training (PRT+FLEX) vs. flexibility training only (FLEX) on physical function in people with RA.

We hypothesized that the 12-week PRT+FLEX program would result in improved physical function and less disability as measured by self-reported questionnaires and performance tests as compared with the 12-week FLEX program.

Objective #2: To explore potential mechanisms associated with improved physical function including changes in body composition and REE in people with RA.

We hypothesized that the exercise intervention would be associated with improved body composition (increased appendicular lean mass and lower body fat), increased muscle strength, and normalization of REE.

1.5 Delimitations

We identified the following delimitations:

1. Participants were between the ages of 18 and 65.

2. Participants were sedentary at baseline

3. Participants were required to have medical clearance and adequate physical function to participate in the PRT program.

1.6 Limitations

These delimitations may lead to the following limitations:

1. The generalizability of these findings is unclear as the study sample was relatively young mostly white, and female with had a high level of functioning.
2. Results may be affected by other factors that were not assessed such as nutrition, sleep habits, and comorbidities.
3. Although self-report measures were used to assess physical activity, many participants were unsure of how many days per week they engaged in moderate, vigorous, or walking activities, which influenced the reliability and validity of these assessments.

Chapter 2 – Review of Literature

2.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by high levels of inflammation, pain, disability, and pre-mature mortality (Uhlig et al., 2014). RA can begin at any time in a person's life, but is usually diagnosed between the ages of 45 and 65 (Swärdh & Brodin, 2016). The disease affects more women than men, and its prevalence is between 0.3% - 1% of the global population (Cross et al., 2014; Lundkvist, Kastäng, & Kobelt, 2008; Uhlig et al., 2014). Although global prevalence rates have decreased, rates in Quebec and Ontario have increased over the last 15 years (Jean et al., 2017; Widdifield et al., 2014). RA incurs significant cost to the individual, the healthcare system, and to society (Boonen & Severens, 2011; Uhlig et al., 2014). In Canada for example, each RA patient annually costs the healthcare system $5,531 (without drugs) (Ohinmaa et al., 2014). When considering the additional costs associated with pharmacotherapy, this number can increase to over $30,000 (Bansback et al., 2017). In total, Canada spends an estimated $3.5 billion annually on RA, 9th on a list of 35 developed countries (Lundkvist et al., 2008).

As diagnostic tools, treatment strategies, and patient care continually improve, RA-associated mortality has declined both globally (9% between 1990 and 2010), and in Quebec (Cross et al., 2014; Jean et al., 2017). Despite these improvements, RA is related to increased disability, and numerous co-morbidities as the risk of cardiovascular disease, osteoporosis, infections, depression, and cancers are all elevated (Hoes, Bultink, & Lems, 2015; Matcham, Rayner, Steer, & Hotopf, 2013; Summers, Metsios, Stavropoulos-Kalinoglou, & Kitas, 2010). It is thought that some co-morbidities (i.e., cardiovascular disease, osteoporosis) are affected by a combination of inflammation, disease activity, and other factors, while the origins of other co-morbidities (i.e., depression), are less clear (Cutolo et al., 2014).

2.2 Comorbidities

Co-morbidities are common in individuals with RA and are associated with increased mortality, poor HRQL, and decreased functional ability (Gullick & Scott, 2011; Marques, Cruz, Rego, & da Silva, 2016). One UK study of nearly 1,500 RA participants (at baseline, mean age was 55.3 (14.6) years, 67% female, mean disease duration was 8.2 (6.0) months) found that after a 15-year follow-up period, the prevalence of co-morbidities increased from 31.6% to 81% (Norton et al., 2012). Although developing co-morbidities would be expected in an aging sample, the rates of common co-morbidities reported by Norton et al. (2012) such as hypertension, and ischemic heart disease were elevated in individuals with RA compared to the general population. Additionally, one-third of participants reported having multiple co-morbidities at baseline which is higher than the US population (25%) (CDC, 2016). Co-morbidities such as fatigue, depression, obesity, and cardiovascular disease may influence each other, and possibly exacerbate the effects of a single condition. For example, for an individual who experiences high levels of pain, physical inactivity and disability may become more common (Stavropoulos-Kalinoglou, Metsios, Koutedakis, & Kitas, 2010). As physical inactivity becomes more routine in the individual's life, metabolic health, and body composition may become compromised as high blood pressure, obesity, and risk factors for cardiovascular disease could also originate (Challal, Minichiello, Boissier, & Semerano, 2016; Stavropoulos-Kalinoglou et al., 2010). This has important consequences as managing multiple co-morbidities is difficult not only for the individual, but places significant burden on the healthcare system.

Fatigue, affecting 72-87% of RA people influences both psychological health, and physical functioning (Bartlett et al., 2018; van Steenbergen, Tsonaka, Huizinga, Boonen, & van der Helm-van, 2015). Interactions between personal (i.e., social support, thoughts, feelings), and disease-related (i.e., disease activity, pain) factors are thought to contribute (Katz, 2017; van Steenbergen et al., 2015). Among 2,000 women with RA, almost 60% of survey respondents said not having fatigue was a "good day" (Strand, Wright, Bergman, Tambiah, & Taylor, 2015). Further, in an 8-year longitudinal study of over 600 RA participants, severe fatigue persisted even when disease activity was controlled (van Steenbergen et al., 2015). Although this was longitudinal in design, a more recent study of nearly 2,200 RA participants showed that fatigue continued to persist despite individuals being in remission or being in low disease activity (Olsen, Lie, Kvien, & Zangi, 2016).

People with RA are at an increased risk of developing depression (Matcham, Ali, Irving, Hotopf, & Chalder, 2016; Matcham et al., 2013). While prevalence estimates vary greatly, a recent systematic review and meta-analysis reported depression to affect nearly 39% of individuals with RA (Matcham et al., 2013). Depression is associated with disease activity both cross-sectionally (Imran et al., 2015) and longitudinally (Matcham et al., 2016) suggesting a link between RA progression and psychological well-being.

The prevalence of obesity and metabolic syndrome are elevated in individuals with RA (Stavropoulos-Kalinoglou et al., 2010; Summers et al., 2010; Zhang et al., 2013). A recent study of 200 RA individuals from Montreal and Winnipeg reported that 34% were classified as obese compared to 25% of the Canadian population using the World Health Organization's criteria (Colmegna, Hitchon, Bardales, Puri, & Bartlett, 2016) In a sample of 131 RA participants and 121 controls, Giles et al. (2010) found that compared to un-matched controls, total fat, and visceral adipose tissue were greater in RA individuals. Further, the increases in adiposity (specifically visceral adiposity) were associated with an increased risk of metabolic syndrome (Giles et al., 2010). A recent meta-analysis concluded that RA individuals have a higher prevalence of metabolic syndrome, and that this is an independent risk factor for cardiovascular disease (Zhang et al., 2013). Finally, one study that explored differences in cardiac risk factors between RA individuals and healthy controls found that not only were RA participants significantly more likely to die from cardiovascular disease ($p = .012$), but to also have recurrent cardiac events ($p = .013$) (Douglas et al., 2006).

2.3 Disability

Despite aggressive treatment strategies, disability (or loss in physical function) still persists in RA (Katz, Morris, & Yelin, 2006; Krishnan, Lingala, Bruce, & Fries, 2011). In a recent review article, it was reported that compared to healthy individuals, people with RA are two times more limited in daily activities and are 30% more likely to need day-to-day assistance (Ma et al., 2014). Preventing future disability is an important aim of treatment as declines in physical function are associated with higher healthcare costs, increased mortality, and poor HRQL (Gong & Mao, 2016; Ji et al., 2017).

RA-related disability results in difficulties carrying out everyday tasks such as cooking, shopping, and child care. One study involving over 500 RA individuals, found that 95% of participants had at least one valued activity that was affected by RA (Katz et al., 2006). These difficulties extend into the workplace as a large portion of the societal costs related to RA are because of poor work participation. People with RA are less likely to be productive at work

(Zhang & Anis, 2011), use more than four times the amount of sick days than the average worker, and are at an increased risk of not being employed (Boonen & Severens, 2011).

Joint damage often begins early in RA, and has been shown to be associated with long-term disability (Bombardier et al., 2012). Other factors such as age, sex, disease activity, treatment, HRQL, and mobility have also been predictive of future disability (De Croon et al., 2004; Krishnan et al., 2011). Researchers have explored how body composition changes that are characteristic of RA are related to physical limitations. Giles et al. (2008) found in a sample of 197 RA participants that increases in appendicular fat mass and losses in appendicular muscle mass were significantly correlated with decreased physical function, while the reverse (losses in appendicular fat, and gains in appendicular muscle) were associated with increased physical function. Specifically, self-reported disability was significantly related to appendicular lean mass ($\beta = -.052$, $p < .001$), and appendicular fat mass ($\beta = .042$, $p < .001$, $R^2 = .091$). The authors suggested that increases in appendicular fat may inhibit range of motion, making everyday activities difficult (Giles et al., 2008). Similarly, in a subset of the sample used by Giles et al. (2008), Kramer et al. (2012) found that higher thigh fat area and lower thigh muscle area were related to lower physical function and higher performance limitations in 152 RA individuals. Further, physical function (measured by the Short Physical Performance Battery) was 63% higher in the group with the highest thigh muscle density and lowest thigh fat area compared to the group with the lowest thigh muscle density and highest thigh fat area (Kramer et al., 2012).

The findings of Giles et al. (2008), and Kramer et al. (2012) were supported by the research of Baker et al. (2014) who explored how fat mass and muscle mass are associated with functional outcomes in 50 RA participants. They reported that muscle density in people with RA was inversely associated with Disease Activity Score (DAS) ($r = -.30$) (Van der Heijde et al.,

1990) and the HAQ (*r* = -.39) (*p* values <.05). All three studies show the intimate relationship between muscle mass, fat mass, and physical function suggesting that improving muscle mass and/or strength may produce beneficial changes in physical function.

2.4 Physical Inactivity and Sedentary Behaviour

Compared to the general population, people with RA have decreased levels of physical activity and aerobic fitness (Henchoz et al., 2012; Sokka et al., 2008). Data from the Swedish RA registry revealed that 47% did not meet physical activity guidelines (Eurenius & Stenström, 2005), while a larger cross-sectional study including 5,200 RA individuals from 21 countries across Europe, the US, and Canada found that only 14% self-reported exercising three or more times per week (Sokka et al., 2008). Importantly, physical activity in both of these studies is significantly lower than the World Health Organization's estimation of global inactivity in the general population (one-third are insufficiently active) (Eurenius & Stenström, 2005; WHO, 2018).

Lower levels of physical activity in RA individuals may result from inflammation, joint pain, and body composition changes (amongst others factors such as fatigue, and disability) (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015; van Zanten et al., 2015). Intuitively, it may make sense to rest when individuals are feeling fatigued and sore, yet physical inactivity can lead to gains in fat, losses in muscle mass, and is also a risk factor for cardiovascular disease, high blood pressure, and metabolic syndrome (Cicero et al., 2012; Laaksonen et al., 2002). In a sample of 107 RA participants (mean age of 55 years, 76% white, 85% female), accelerometers revealed that on average, participants achieved nine minutes of moderate-vigorous intensity per day (Semanik et al., 2010). This is far below the moderate-vigorous physical activity recommendations of 150 minutes per week (WHO, 2018). In a recent study of 61 RA individuals, accelerometry was used to determine sedentary behaviour and activity intensities throughout a week. It was found that sedentary time was significantly associated with an increased 10-year cardiovascular disease risk, while light-intensity activity was associated with a reduced risk (Fenton et al., 2017). The results of Fenton et al. (2017) show how influential sedentary time (and physical activity) is to cardiovascular disease risk, offering an opportunity for future interventions to target both activity promotion, and sedentary time reduction in people with RA.

2.5 RA Inflammation

As research has progressed, the pathogenesis of RA has become more clear, and is now known to involve the actions of many different inflammatory cytokines (McInnes & Schett, 2011). These cytokines such as TNF-α, IL-1β and others appear to shift protein metabolism towards muscle breakdown (Walsmith & Roubenoff, 2002). Although this is an acute adaptive response to promote survival (the body begins to use protein as an energy source), these responses can lead to long-term decreases in muscle mass, strength, and physical function (Walsmith & Roubenoff, 2002). Interestingly, inflammatory cytokines such as TNF-α and IL-6 are also secreted by adipose tissue (Stavropoulos-Kalinoglou et al., 2010), which may suggest that as muscle wastes and fat begins to accumulate, there may be an increase in the harmful inflammatory proteins that contribute to swelling, pain, and disease progression.

2.6 Altered Energy Expenditure Profiles

Altered energy expenditure can result in caloric imbalances which could lead to future adverse health outcomes (Koplan & Dietz, 1999). For example, if caloric intake is consistently higher than caloric output, weight gain occurs, which could lead to other long-term health complications such as obesity, hypertension, and cardiovascular disease (Koplan & Dietz, 1999). Further, altered energy metabolism may make it difficult for healthcare practitioners to monitor components of energy expenditure. Metsios et al. (2008) noted the importance of having accurate energy expenditure predictions that could be incorporated into clinical care, and developed RA-specific equations to better predict resting metabolism (Metsios, Stavropoulos-Kalinoglou, Panoulas, et al., 2008).

Total energy expenditure (TEE) is the total amount of calories used by the body each day, and consists of the thermic effect of food (TEF), resting energy expenditure (REE), and physical activity energy expenditure (EEPA) (Ravussin, Burnand, Schutz, & Jequier, 1982). In healthy individuals, energy balance can be explained by the following equation (percentages indicate relative contribution) (Ravussin et al., 1982):

$$TEE = TEF\ (\sim 15\%) + REE\ (\sim 70\%) + EEPA\ (\sim 15\%)$$

TEF is the amount of energy required for digestion and can be estimated (traditionally 10 – 15% of TEE) or measured via indirect calorimetry. Objective measurements of TEF begin with an REE assessment, followed by a standardized meal, and then another three-six hour indirect calorimetry assessment to note the difference in energy expenditure in a fasted and fed state (Reed & Hill, 1996). There has been no evidence thus far that suggests modifications to TEF estimates are needed in RA individuals (Marie Tierney, Fraser, Purtill, & Kennedy, 2015).

REE is the energy required for the body to function at rest and can be measured objectively via indirect calorimetry or predicted from equations (i.e., Harris-Benedict equation) that typically take height, weight, sex, and age into account (Hall et al., 2012). Indirect calorimetry is time consuming, involves expensive equipment, and requires trained personnel, while predictive equations are simple and fast (Ainslie, Reilly, & Westerterp, 2003). They may however be misleading as normal formulas do not take into account the metabolic alterations or body composition changes characteristic of RA (Metsios, Stavropoulos-Kalinoglou, Panoulas, et al., 2008). EEPA is the energy used through physical activity, and can be assessed by standardized questionnaires (such as the International Physical Activity Questionnaire) (Craig et al., 2003) or via objective measurements such as pedometers or accelerometers (Hills, Mokhtar, & Byrne, 2014).

The importance of accurately determining energy expenditure in RA individuals is significant, as some studies, and one review paper have reported that inflammation is related to a state of hypermetabolism increasing REE (Challal et al., 2016; Roubenoff et al., 1994; Walsmith, Abad, Kehayias, & Roubenoff, 2004). In one recent study of 57 RA individuals, REE assessed via indirect calorimetry was significantly related to disease activity (DAS; $\beta = +.21$, $p = .02$), suggesting a link between hypermetabolism, inflammation, and disease progression (Hugo et al., 2016). This is in line with past research that has reported a link between cytokine production, and REE (TNF-α: $\beta = 213.1$, $p < .001$ and IL-1β: $\beta = 287.2$, $p < .001$) (Roubenoff et al., 1994). Further, hypermetabolism and increased disease activity have both been associated with decreased fat-free mass (Binymin, Herrick, Carlson, & Hopkins, 2011; Walsmith et al., 2004), illustrating the negative effects increased inflammation could have on muscle mass (and therefore strength and physical function). The ongoing cycle of elevated inflammatory cytokines, muscle breakdown, and decreased strength have significant implications for people with RA as they may become more susceptible to co-morbidities, have decreased physical function, and have lower HRQL.

One of the most modifiable aspects of TEE is EEPA, yet because of inflammation, joint pain, and reduced muscle mass, EEPA has been shown by some researchers to be lower in people with RA compared to healthy controls (Mancuso, Rincon, Sayles, & Paget, 2007; Marie Tierney et al., 2015). Roubenoff et al. (2002) determined that in 20 RA women, EEPA was 27% lower (~1000 kJ/day) compared to controls. Similarly, Mancuso et al. (2007) found that in 121 RA individuals and 120 controls, RA participants expended fewer kilocalories per week in total walking time and in total activity. Further, RA people were 16% less likely to meet walking recommendations of more than 700 kilocalories per week (Mancuso et al., 2007). The results of Roubenoff et al. (2002) and Mancuso et al. (2007) both provide evidence for possible energy expenditure imbalances that exist in people with RA. Roubenoff et al. (2002) stated that the energy imbalance typical of an RA participant in their study would lead to a 15-kg gain in body weight over a 10-year period which could have implications for the development of obesity, and other chronic conditions. Although REE has been shown in some studies to be higher in RA than in healthy controls (Roubenoff et al., 1994; Walsmith et al., 2004), the large decrements in EEPA ultimately reduce TEE (Henchoz et al., 2012; Tierney, Fraser, & Kennedy, 2012). This could result in weight gain, and long-term adverse health outcomes when coupled with hypermetabolism, and the other physiologic changes occurring in the body which are characteristic of RA.

2.7 Rheumatoid Cachexia

Rheumatoid cachexia (RC) is a devastating cycle of muscle breakdown, and fat gain that has significant implications on physical activity levels, physiologic health, and HRQL (Challal et al., 2016; Walsmith & Roubenoff, 2002). Importantly, RC is associated with increased disability, and may not be noticed during clinical examinations (Arshad, Rashid, & Benjamin, 2007).

Body cell mass (BCM) is a major component of fat-free mass consisting mainly of skeletal muscle, and plays a significant role in daily activities, and physical function (Walsmith & Roubenoff, 2002). Only a 5% loss in BCM can result in significant decreases in strength, and metabolic alterations, while losses of more than 40% can cause death (Arshad et al., 2007). Among 23 RA individuals and 23 healthy controls, Roubenoff et al. (1994) found 13% less BCM than healthy-matched controls. A decade later, Walsmith et al. (2004) found that in 20 women with well-controlled RA, BCM was 14% less than healthy controls and that BCM was inversely correlated with inflammation. These results strengthened earlier findings that reported elevated REE and decreased BCM in RA individuals (Roubenoff et al., 1994; R. Roubenoff, Roubenoff, Ward, Holland, & Hellmann, 1992).

Over the last decade, treatment strategies have impacted the hypermetabolism first described in the late 20th century. In a recent study of 57 RA individuals (mean age was 58 (10) years, 73% female, disease duration of 4 (3) years, DAS was 3.9 (1.8)), REE was not elevated in those who were found to be cachectic compared to non-cachectic (Hugo et al., 2016). Additionally, a recent review suggests RA-inflammatory molecules play a large role in markers for disease status, and in the development of chronic conditions (Chimenti et al., 2015). Although the review does mention altered metabolism, the authors state that pharmacotherapy is advancing to suppress systemic inflammation, which could possibly mitigate the hypermetabolic state introduced nearly 25 years ago.

There are different definitions of RC as there is some debate about exactly what constitutes it. Some researchers use fat-free mass index (FFMI) (fat-free mass, kg/height^2) and fat mass index (FMI) (fat mass, kg/height^2) to distinguish between cachectic, and non-cachectic people (Elkan, Håkansson, Frostegård, Cederholm, & Hafström, 2009; I. L. Engvall et al., 2008), while a more recent definition uses appendicular lean mass index (ALMI Z Score = Actual ALMI Z Score – Predicted ALMI Z Score * (1/SD)) (Weber, Long, Leonard, Zemel, & Baker, 2016). Engvall et al. (2008) defined cachexia as a FFMI below the 10^{th} percentile and a FMI above the 25^{th} percentile, while other researchers used FFMI and FMI thresholds of below the 25^{th} and above the 50^{th} percentile respectively (Elkan et al., 2009).

Additionally, to more accurately account for the losses in muscle mass and gains in fat mass that occur through RC, some suggest modifying BMI thresholds for overweight and obese RA individuals (from 25 kg/m^2 to 23 kg/m^2 and 30 kg/m^2 to 28 kg/m^2 respectively) (Stavropoulos-Kalinoglou et al., 2007). These suggestions to alter BMI cut-points were supported by more recent research which reported similar recommendations in a sample of 141 RA participants (mean age was 58 (10.8) years, 60% female, mean disease duration of 19 (11) years) (Katz et al., 2013).

Treatment guidelines from the European League Against Rheumatism (EULAR) recommend starting conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) as soon as an RA diagnosis has been made (Smolen et al., 2017). csDMARDs aim to suppress inflammation, and mitigate joint damage, yet some people do not respond to them (Siebert, Tsoukas, Robertson, & McInnes, 2015). In two studies of 20 (Metsios et al., 2007), and 26 RA individuals (Marcora, Chester, Mittal, Lemmey, & Maddison, 2006), anti-TNF-α therapy reduced disease activity but reduced disease activity had no subsequent effect on body composition. Finally, in a recent review of anti-TNF-α therapy and weight gain, the authors state that most RA studies in their review reported an increase in fat mass, visceral fat, or total fat while using anti-TNF-α therapies. (Peluso & Palmery, 2016).

Although biologic therapies have shown benefit in inhibiting joint destruction, and suppressing disease activity, they are very expensive ($15,000 - $30,000 annually per patient), and have significantly increased the economic burden associated with RA (Bansback et al., 2017). Recent care has emphasized the aggressive and continual monitoring of disease activity with the end goal of remission (Bykerk et al., 2012). In a recent study by Lemmey et al. (2016), 82 RA individuals were treated in this fashion and body composition (muscle mass and fat mass) did not improve.

Dietary supplementation in people with RA has not been extensively investigated, and even less is known about its possible effects on RC. Creatine supplementation has been used to increase muscle strength and physical function, although research has yielded conflicting results. In one study, 3 weeks of creatine supplementation showed increases in muscle strength but had no effect on physical function or disease activity (Willer, Stucki, Hoppeler, Brühlmann, & Krähenbühl, 2000). In contrast, a recent study found that 12 weeks of creatine supplementation increased muscle mass, but not muscle strength (Wilkinson et al., 2016). Future studies are needed to study the potential of creatine supplementation to increase muscle mass and strength for RA individuals.

As new research explores the role of the gut's microbiome in RA development, it has been hypothesized that dietary changes can affect inflammation and disease activity directly (Badsha, 2018; Rudbane et al., 2018). In response to this, the potential effects of probiotics to reduce inflammation and improve disease activity have recently been explored. One meta-analysis found that TNF-α, IL-1β, and IL-6 did not significantly change with probiotic use, but disease activity improved (Rudbane et al., 2018). Another meta-analysis however, reported that IL-6 levels differed with probiotic use but disease activity score remained unchanged (Mohammed et al., 2017). Future studies should investigate concurrent dietary supplementation with exercise as it is possible that the combined influence may promote significant changes in muscle mass, strength or other important patient-related qualities such as physical function, and HRQL.

2.8 Benefits of Exercise in RA

Exercise, or structured physical activity, has numerous physiologic, psychologic, and social benefits (ACSM, 2013). Exercise increases muscle strength and endurance while also promoting cardiac adaptations that reduce the risk of cardiovascular disease, and overall mortality (ACSM, 2013). Additionally, exercise has also been shown to decrease anxiety, depression, and improve well-being and physical function (ACSM, 2013; Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015). Thus, exercise offers a unique opportunity to potentially ameliorate some of the specific health-related issues associated with RA.

As RA progresses, physical limitations and disability may become more pronounced, however, exercise has been shown to improve some of the negative consequences associated with RA (i.e., worsened body composition, higher levels of fatigue, etc.) (Baillet, Vaillant, Guinot, Juvin, & Gaudin, 2011; Metsios & Lemmey, 2015). As exercise improves physical functioning (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015), these benefits would not only enhance daily activities, but could improve patient's psychological well-being, and HRQL. An emerging theme in one qualitative study of 16 physically active RA individuals was that exercise promoted autonomy and social belonging (Loeppenthin et al., 2014). In the same study, one woman stated, "It means a great deal to me not seeing my body as being ill and physically handicapped, but also experiencing a body being strong and feeling good".

Exercise has also been shown to mitigate RA symptoms including fatigue, stiffness, and pain. Fatigue and pain are both major barriers to physical activity in RA and are closely related to psychological well-being (Pollard, Choy, Gonzalez, Khoshaba, & Scott, 2006). Once fatigue, stiffness, and pain are overcome, exercise can significantly reduce both fatigue and pain (Baillet et al., 2010; Metsios & Lemmey, 2015; Rongen-van Dartel et al., 2015).

Finally, exercise also may alter energy expenditure components, which is of particular importance in RA. Although only studied once in RA, much is still unknown about the potential role exercise may have in altering energy expenditure. Exercise would be expected to increase the TEF (because of an increased need to replenish muscle glycogen) (Denzer & Young, 2003), EEPA (if participants continue with their usual physical activity habits), and possibly increase or decrease REE (may increase because of the changes in fat-free mass, but may decrease because of the already hypermetabolic state). Overall, TEE would still be expected to increase with exercise (because of the strong contribution of EEPA), but may not change depending on the large relative contribution of potential REE changes.

2.9 Aerobic and Combined Exercise

There are many different ways people with RA can exercise and be active depending on personal preference, environment, and physical limitations. Typically, recommendations for aerobic exercise are consistent with those of healthy, age-matched individuals as walking, cycling, and dancing can be completed three to five times per week, in periods of 5-30 minutes (ACSM, 2013). In people with RA, aerobic exercises have been shown to improve aerobic fitness, reduce cardiovascular disease risk, and anxiety (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011), and can also be used to target fatigue, one of the most debilitating symptoms of RA (Rongen-van Dartel et al., 2015). In a meta-analysis of five randomized controlled trials in RA, land-based aerobic training programs improved fatigue in the short term (both 12 and 24 weeks) (Rongen-van Dartel et al., 2015).

For those who may have vulnerable joints, or who don't enjoy walking, cycling or running, water-based activities such as swimming are a good alternative to still attain aerobic benefits (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011). Water-based activities (i.e., two 30-minute sessions for four weeks) have been shown to reduce joint discomfort and increase psychological well-being (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011). There is also evidence that a lifestyle promoting physical activity such as increasing walking can also provide positive health outcomes to RA individuals, including improved cardiovascular health (Mancuso et al., 2007; Metsios & Lemmey, 2015; Metsios, Stavropoulos-Kalinoglou, van Zanten, et al., 2008).

Although there are recognizable benefits of aerobic exercise for people with RA, not all exercise related adaptations may help to reverse RC. For example, many aerobic exercise studies have not investigated body composition changes in response to aerobic training (Baillet et al., 2010; Neuberger et al., 2007; Scarvell & Elkins, 2011). Similarly, there is limited evidence that aerobic exercise would increase muscle strength as a review by Swardh et al. (2016) found that short-term (8-12 weeks) aerobic land-based exercise resulted in an increase in VO_2max but not an increase in muscle strength. As people with RA typically have lower aerobic capacities, the intensities conducted in previous studies may be too low to produce changes in key body composition metrics or muscular strength measures. Thus, for building muscle, and developing strength, aerobic exercise may not be optimal.

Alternatively, a combination of aerobic exercise and resistance strength training to increase muscle strength and aerobic fitness levels is recommended (Cairns & McVeigh, 2009;

Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015; Stenström & Minor, 2003). Combined exercise programs of different durations, and intensities have been shown to have beneficial effects in RA. For example, combined programs have lasted between four weeks and two years, used sports and different exercises, and in some cases, favoured more aerobic activity than resistance training (Baillet et al., 2009; de Jong et al., 2003; Stavropoulos-Kalinoglou et al., 2013; Strasser et al., 2011). What is consistent with most combined exercise studies are the statistically significant improvements in aerobic fitness (+17-27%), and DAS (- 22-23%), and clinically significant improvements in physical functioning (change in HAQ scores of .22) (Baillet et al., 2009; de Jong et al., 2003; Stavropoulos-Kalinoglou et al., 2013). Other combined training programs, have reported statistically significant increases in muscle strength (9 - 22%), reductions in body fat percentage (7 - 8%), and improvements in lean body mass (+3%) (Stavropoulos-Kalinoglou et al., 2013; Strasser et al., 2011).

Combined training is recommended for RA individuals because it offers a wide range of cardiovascular, and muscular benefits that wouldn't be attained with one program or the other. It does however, pose a significant question as to what component of the program is targeting cachexia. For example, in the Stavropoulos-Kalinoglou et al. (2013) study, body fat was significantly reduced from baseline to month three, the time corresponding to only aerobic exercise. When resistance exercises were introduced in conjunction with aerobic exercises (at month three to month six), significant improvements were again seen in body fat percentage. With this study design, it's impossible to identify what led to the declines in fat mass from months three to six as it's possible that the aerobic exercise, the resistance exercise, or both led to the fat mass decrements. If reversing the negative body composition changes and decrements in muscle strength are the aim of exercise, then having a program that specifically targets muscle hypertrophy may be more advantageous to promoting physiologic benefits, especially in individuals with RC.

2.10 Resistance Training

Recommendations for resistance training are similar to those of the healthy population (i.e., two to three times per week, for two to three sets of 10-15 repetitions) (ACSM, 2013; Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015). Using weight machines, free-weights, and resistance bands are recommended for RA individuals (Flint-Wagner et al., 2009; Metsios & Lemmey, 2015; Stenström & Minor, 2003). Exercises that target larger muscle groups (i.e., chest, back, quads and glutes) require greater energy outputs and result in greater increases in muscle mass, and strength compared to exercising smaller muscle groups (ACSM, 2013).

To date, seven studies have evaluated the effects of resistance training in RA individuals, and have specifically evaluated changes in muscle strength, body composition, and/or REE. These studies are described in detail below and shown in Table 1.

Prior to 1996, some studies investigated the effects of exercise and RA, but they were either combined training (Häkkinen, Häkkinen, & Hannonen, 1994), had low training intensities (Lyngberg, Ramsing, Nawrocki, Harreby, & Danneskiold-Samsøe, 1994) or failed to report specific information about the exercise intervention (Nordemar, 1981). Rall et al. (1996) explored the effects of a 12-week resistance training program in eight RA participants (5 females, 41.8 (12.6) years, disease duration of 14.6 (12.5) years, mean pain of 5.5 (3.5), and a HAQ disability score of 1.0 (.8)), eight healthy young subjects (25.8 (2.5) years), and eight healthy elderly subjects (70.3 (5.0) years). Twelve weeks of high intensity strength training (completed twice per week) improved muscle strength, walk speed, balance, self-reported pain (21%), fatigue (38%), and did not change REE as measured by indirect calorimetry. Despite being 30 years younger at baseline, RA individuals had lower strength scores in chest press, leg press, and leg extension compared to all other groups. By the end of the 12-week program, RA participants had the highest relative improvement from baseline in chest press (54%), leg press (74.8%), leg extension (53.5%), back extension (58.3%), and abdominal curl (56.9%). Although these results may suggest a level of deconditioning in RA participants, it is important to note that at post-testing, RA participants showed similar strength outputs compared to healthy controls.

This study did possess limitations, as muscle strength was assessed through the repetition of the same exercises being completed every training session. Naturally, neuromuscular adaptations would improve scores after the continual repetition of the same exercises. Additionally, the training intensity (five exercises for three sets of eight repetitions each workout) was relatively low, possibly mitigating some of the potential resistance training effects on REE. The findings of this study were the first to suggest that resistance training may improve muscle strength, fatigue, and pain ratings, without negatively affecting disease progression or disease status.

Van den Ende et al. (2000), investigated the effects of an in hospital exercise program (mean (SD) length = 30 (14) days). The intensive exercise program investigated the effects on muscle strength, pain, and physical function, and followed participants for 24 weeks. This study had a sample of 64 participants with a mean age of 60 (13) years, and a mean disease duration of 8 (8) years. Participants were randomly assigned to a conservative program (range of motion exercises, and body weight isometric exercises) or an intensive exercise program (Van den Ende et al., 2000). The intensive program required participants to complete knee and shoulder dynamometer exercises five times per week in addition to range of motion and isometric exercises. Intensive participants also cycled three times per week for 15 minutes. After 24 weeks, the intensive program resulted in improvements in DAS (-1.4 (1.5)), 50-foot walk test (decreased by ~30%), and clinically relevant improvements in the HAQ (- 0.5 units).

The longest resistance training intervention was conducted over two years and explored changes in muscle strength, bone density, and physical function (Häkkinen, Sokka, Kotaniemi, & Hannonen, 2001). In this study, 70 RA participants were randomly assigned to range of motion or strength training (50-70% of maximum targeting major muscle groups). Participants were instructed to complete exercises twice per week (two sets per exercise, 8-12 repetitions) and were not supervised for the study duration (self-report compliance). Thirty-one participants (18 females, mean age = 49 (10) years) completed the resistance training program, and showed improvements in knee extensor muscle strength (44%), trunk extension (19%), trunk flexion (24%), grip strength (50%), and walking speed (26%) (Häkkinen et al., 2001). Unfortunately, investigators told participants to increase activity levels during the study, but did not monitor the physical activity change. This poses a significant challenge in interpreting the results of the study, as improvements in walking speed, and strength could have been attributed to the increase in activity, and not necessarily by the resistance program.

Marcora et al. (2005) evaluated a resistance training program using a two-group, matched controlled, pre-post study design. Ten RA participants were allocated to an exercise group (mean age = 53 (10) years, BMI = 27.9 (4.6) kg/m^2, disease duration = 8.9 (5.7) years), while ten age- and sex-matched RA participants were allocated to a control group (mean age = 54 (10) years, BMI = 29.1 (2.2) kg/m^2, disease duration = 7.3 (5.3) years). The exercise program involved 8 different exercises a session, completed for 3 sets of 8 repetitions, 3 times a week for 12 weeks. The control group continued their usual care, with no additional exercise training. The primary outcome of this study was appendicular lean mass, while secondary outcomes were changes in fat and lean tissue mass in other body regions, physical function, and disease activity. Body composition was measured using the DXA scanner, while muscle strength (elbow flexor, hand-grip and knee extensor) was assessed through a dynamometer. The exercise group had significantly increased fat-free mass (p = .004), appendicular lean mass (arms, p = .005; legs, p = .001), and significantly decreased body fat percentage (p = .047), compared to the control group after the 12-week program. Statistically significant improvements in physical function tests including hand-grip strength (p = .045), elbow flexor strength (p = .016), 30-second sit-to-stand test (p = .001) were also reported, while knee extensor strength was trending towards significance (p = .073).

Lemmey et al. (2009) randomized 28 RA individuals to either a progressive resistance training program (twice weekly, 24 weeks) or a range of motion control group (exercises completed twice per week at home). Participants in the resistance training group (n = 13) were mostly female (11), were 55.6 (8.3) years old, had a disease duration of 74 (76) months, and a DAS of 3.3 (1.3). The exercise program consisted of 3 sets of 8 repetitions of leg press, chest press, leg extension, seated rows, leg curl, triceps extension, standing calf raises, and bicep curls at 80% of maximum load which was reassessed every 4 weeks. Importantly, to familiarize participants with exercises and lifting techniques, this study implemented an introductory 2-week period. The 24-week resistance training program was associated with significantly increased lean body mass (p = .006), appendicular lean mass (p = .002), training-specific strength (119%), and knee extensor strength (25%). Other objectively measured physical function tests that showed significant improvements were the 30-second chair stand test (30%), 30-second arm curl test (23%), and 50-foot walk test (17%).

The Marcora et al. (2005) and Lemmey et al. (2009) studies both showed statistically significant improvements in lean tissue mass, which is in contradiction to the findings of Rall et al. (1996). One possible reason for the discrepancy is the training volume in the Rall et al. study (2,800 repetitions), was significantly lower than the Marcora et al. (6,912 repetitions) and Lemmey et al. (10,224 repetitions) studies despite being at similar intensities. This may have influenced not only body composition, but also the lack of REE change reported by Rall et al. (1996).

Flint-Wagner et al. (2009) explored the effects of a 16-week resistance program on muscle strength, pain, and physical function. Twenty-four RA people were randomized in a 2:1 ratio to either strength training (mean age = 52.2 years, BMI = 26.7, RA duration = 15.4 years) or a control group (mean age = 49.0 years, BMI = 26.0, RA duration = 11.2 years). The exercise intervention targeted major muscle groups at an intensity of 70-85% 1-repetition maximum (1RM). Each exercise was completed for 2 sets of 6-8 repetitions, 3 times a week for 12 weeks. This study is unique as the researchers allowed the participants to have a choice of 3 different exercise difficulties depending on their level of muscle soreness, pain, and daily fatigue. The exercise options ranged from using resistance bands, to weight machines, to dumbbells. The authors reported an increase in total strength of 46.1 (31.6) % from all 3-RM exercises (i.e., leg press, hammer curl, and incline dumbbell press). The increase in 3-RM however, likely resulted from exercise repetition, beyond true strength adaptations as these exercises were routinely being conducted at each workout session (similar to Rall et al. (1996)). Additional significant changes were found in right grip strength ($p = .06$), and 50-foot walk times (-9%, $p = .01$), while reductions in pain (-53% using a VAS, $p = .07$) were trending towards significance. Clinically significant changes were seen in self-reported disability (HAQ - 0.4). This study is distinct because it evaluated the effects of having flexible exercise routines that could accommodate disease activity, pain, and soreness.

Morsley et al. (2017) recently explored the feasibility of providing a group resistance training program to RA individuals from a physiotherapy department in a general hospital. The 6-week progressive resistance training group program included 83 RA individuals at baseline (mean age = 51 years, 60% female) who attended supervised group exercise sessions once a week (8-10 people per group). Participants were also instructed to complete two additional exercise training sessions between classes. After six weeks, statistically significant changes in waist circumference (-1.6 (7.3) cm), hip circumference (-1.0 (4.6) cm), body fat percentage (-0.7 (8.2) %), grip strength (3.0 – 3.1 kg), single leg stance (2.00 (7.8) seconds), HAQ (-.24 (.62)), and VAS (-7.8 (20.2)) were reported (all comparisons less than $p < .005$). This study did possess some limitations, as the drop-out rate was very high (33%), and did not report attendance values for participants. This study showed that a simple, short-term, group workout program conducted once a week with twice weekly home practice can improve body composition, and strength in a sample of RA people.

Combined, these studies show the safety and efficacy of progressive resistance training to reverse changes in body composition, muscle strength, and physical function in people with RA. The summaries, and additional information of the resistance training studies are displayed in Table 1.

Table 1. Summary of key resistance training studies in people with rheumatoid arthritis.

Year	N	Intervention	Measures	Outcomes	Limitations
Rall et al., 1996	8 RA adults: Mean age = 42 years, 5 female BMI = 25 RA duration = 15 8 healthy adults and 8 older adults also exercised 6 older adults were controls	12-week high intensity resistance exercises 2x/week, 3 sets of 8 reps for each of the five exercises (chest press, leg press, leg extension, back extension, abdominal curl) 80% 1RM; retested every 2 weeks	Max VO_2 DXA for body comp REE via indirect calorimetry HAQ Pain VAS Balance and gait 50 foot walk test Geriatric depression scale ESR	↑ muscle strength (54-75%) ↓ 50-foot walk time ↓ pain and fatigue No change in muscle or fat mass No change REE 87% of training sessions completed No training-related injuries Energy intake increased 300 kcal/d	No control group Training volume inadequate to induce muscle growth
van den Ende et al., 2000	64 people randomized to intensive exercise or control group Exercise: Mean age = 62 years, 59% females, RA duration = 8 years	All participants completed range of motion and body weight isometric exercises (4 times per week, for their in-hospital stay, mean duration = 30 (14) days) Exercise group participated in dynamometer knee and shoulder exercises (3 sets, 5 repetitions, at 70% 1RM, 5 times per week) and cycled (15 minutes, 3 times per	DAS Pain VAS ESR HAQ 50-foot walk test Dynamometers for KES, knee flexor strength	↓ DAS (-1.4) ↓ Pain VAS (-1.75) ↓ HAQ (-0.5) ↑ KES ↓ 50-foot walk test (-7.6 seconds)	Sample bias: Large amount of people lost to follow-up Did not include possible confounders (i.e., physical activity and diet) into study design

	Control: Mean age = 58 years, 66% females, RA duration = 7 years	week)			
Hakkinen et al., 2001	62 people were randomized to exercise or control group Exercise: Mean age = 49 years, 58% females RA duration = 10 months Control: Mean age = 49 years 65% females RA duration = 8 months	Twice a week exercises for 24 months (minimally supervised) 2 sets per exercise, 8-12 repetitions per set (50-70% 1RM) using resistance bands and dumbbells	Dynamometer for KES, trunk muscles, grip strength DXA for body composition HAQ 30-m walk test DAS VAS Pain	↓ DAS (50%) ↓ HAQ (78%) ↑ Pain VAS (67%) ↑ KES (59%) ↑ Trunk extension (19%) and flexion (24%) strength ↑ Grip strength (50%) ↑ Walking speed (26%)	Self-reported exercises Missing physical activity changes
Marcora et al., 2005	20 people were allotted to exercise group or control group	12-week progressive resistance training (3 times per week) Exercise program included 3 sets of 8 repetitions (80%	DXA for body comp Bioelectrical impedance for intra- and extra cellular water volumes	↑ fat-free mass (2%) ↑ total body protein (6%) ↑ total arm protein (6%) ↑ total leg protein (6%) ↑ lean mass (2%) ↓ body fat % (2%)	Treatment was not randomly allocated Low power

	60% female Training Group Mean age = 53 years RA duration = 9 years BMI = 28 HAQ = 1.3	1RM) with 8 exercises (Leg Press, Chest Press, Leg Ext, Seated Row, Leg Curl, Triceps Pushdown, Standing Calf Raise, Biceps Curl). 1- to 2-min rest periods between sets and exercises. 1RM was assessed at the end of Week 0 and every 2 weeks	Dynamometers assessed muscle strength 30-s maximal sit-to-stand test Modified HAQ ADL scale Fatigue VAS ESR	Trend for loss of fat mass in the trunk No exacerbation of disease activity Changes in body composition were associated with improvements in various measures of physical function	No placebo group (i.e., flexibility) Selection-bias: exclusion of severely disabled participants
Lemmey et al., 2009	PRT (n = 13) Mean age = 55.6 years 85% female RA duration = 74 months DAS28 = 3.29 Range of motion (n=15) Mean age = 60.6 years 80% female RA duration = 125 months DAS28= 3.29	PRT group trained twice a week for 24 weeks Exercise Program: 3 sets of 8 reps with a load = 80% of the 1-RM 1–2-minute rest Exercises: leg press, chest press, leg extension, seated rowing, leg curl, triceps extension, standing calf raises, and bicep curl	DXA for body comp Bioelectrical impedance for extracellular and total body water Dynamometer for isometric KES Senior Fitness Test Multidimensional HAQ Pedometers for physical activity Muscle biopsies and blood samples DAS28 ESR Dynamometer for extension and flexion of	Compliance to training = 73% ↑lean body mass (4%) ↑ ALM (8%) ↓ trunk fat mass (18%) ↑ training-specific strength (119%) ↑ chair stands (30%) ↑ knee extensor strength (25%) ↑ arm curls (23%) ↑ walk time (17%) ↑ IGF-1 and IGF binding protein 3 Changes in lean body mass and regional lean mass associated with changes in function	Less disabled sample than would be expected for outpatients

			elbow and knee		
Flint-Wagner et al., 2009	PRT (n = 16) Mean age = 52.2 years RA duration = 15.4 BMI = 26.7 Control (n = 8) Mean age = 49 years RA duration = 11.2 BMI = 26.0	PRT group trained 3 times per week for 16 weeks Program: 70-85% 1RM for 2 sets of 6-8 repetitions. Individualized training program Exercises: leg press, leg curl, hip abduction, hip adduction, calf raises, incline press, row, and hammer curl	50-foot walk test HAQ VAS for pain	↑ total strength (31%) ↑ exercise-specific strength ↑ walk speed (95) ↓ pain (53%) Significant correlations were found in changes in pain and function, and in strength	Neural and muscular familiarity may have resulted in significant gains in exercise specific activities (no strength delay to account for neural adaptations)
Morsely et al., 2017	83 participants Mean age = 51 years 60% female 33 (40%) had established RA 29 (35%) had early RA	Feasibility study in physiotherapy department in general hospital 6 week PRT in groups up to 10 participants Included 8-10 total body exercises (wall slides, chest press, leg extension, leg press, rowing, balance board work, triceps extension, bicep curls, standing calf raises, and step-ups) 30-60 minute classes, once	Waist and hip circumference Skinfold calipers for body fat percentage Right and left grip 60-second-sit-to-stand Single-leg stance HAQ Sleep (participants were asked how they were sleeping) Fatigue Questionnaire Pain VAS	All Participants: ↓ waist and hip circumference (-1.58 and -1.00 cm respectively) ↓ body fat (-.71%) ↓ BMI (-1.78) ↑ right grip (3.04 N) ↑ left grip (3.13 N) ↑ single-leg-stand time (1.5 s) ↓ HAQ (-.24) ↑ Sleep quality ↓ Pain VAS (-8) Early RA Participants:	Participants may have self-selected by not attending or dropping out Participants were told to increase activity levels outside of the study, this may have confounded the results

	per week (Participants were also encouraged to exercise twice a week additionally) 3 sets, 8-12 repetitions		↓ waist circumference (-3.02 cm) ↓ body fat (-1.82%) ↓BMI (-.09) ↑ right grip (2.36 N) ↑ left grip (3.07 N) ↑ single-leg-stand time (3.40 s) ↓ HAQ (-.24) ↑ Sleep quality ↓ pain VAS (-4.46)

All values are presented as means (or mean changes where appropriate) unless specified. ALM= Appendicular lean mass, BMI= Body Mass Index, HAQ = Health Assessment Questionnaire, DXA = Dual-energy- X-ray absorptiometry, 1RM = 1-Repitition Maximum, ESR= Erythrocyte Sedimentation Rate, REE = Resting Energy Expenditure, IGF = Insulin Growth Factor, DAS = Disease Activity Score, KES = Knee Extensor Strength, PRT= Progressive resistance training, VAS = Visual Analogue Scale, ADL = activities of daily living.

2.11 Exercise Programming and Implementation

Developing safe and effective exercise programs for people with RA is important because of the unique day-to-day changes (i.e., pain, stiffness, disease activity) and the challenge of long-term adherence many people experience (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011). Factors that must be considered include current disease status, disease history, comorbidities, overall well-being, physical function, fatigue, exercise history, and personal interests and preferences (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015). Many studies have shown that exercise in varying durations, intensities and forms is both safe and beneficial for people living with RA (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; de Jong et al., 2003; Häkkinen et al., 2001; Lemmey et al., 2009; Marcora et al., 2005), but higher intensity exercises offer greater benefits than lower intensity exercises (Cairns & McVeigh, 2009).

Exercise should be initially supervised, and progressive in nature (incremental steps in intensity and/or duration) (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015). High-intensity training, or other forms of vigorous exercise are not recommended for someone experiencing a flare (ACSM, 2013), while individuals experiencing some discomfort should still engage in light-intensity movements (Metsios & Lemmey, 2015). For people with sore joints or muscles, non-percussive exercises such as stretching, or water-based activities may be appropriate. For those overcoming a flare, people can slowly progress to a more vigorous, weight-bearing exercise program once the disease is well controlled (ACSM, 2013). Individuals who are not familiar with exercise should be shown how to properly execute exercises (i.e., proper form, and range of motion) and to adapt exercises (i.e., more or less challenging variations depending on how they are doing) to minimize the likelihood of injury

(Metsios, Stavropoulos-Kalinoglou, & Kitas, 2015). For example, showing people different variations of the same exercise (i.e., one body weight version, one resistance band version, one weighted version) would teach the individual how to properly complete the exercise and allow them options as to which difficulty is appropriate at that time.

2.12 Summary

RA is a chronic autoimmune disease that affects 1% of the population. Co-morbidities are common in people with RA as diabetes, cardiovascular disease, fatigue and depression are elevated compared to the general population. Even with aggressive treatment strategies, disability is persistent in individuals with RA, and has been a source of major personal, social, and economic burden. Disability influences HRQL, and activities of daily living; rates of physical inactivity are also higher in RA individuals compared to healthy controls. Further, as a result of inflammation and lower levels of physical activity, energy metabolism may be shifted in people with RA. This shift has important consequences in reducing muscle mass, strength, and ultimately affecting physical function. Although treatment strategies have improved disease activity, the cachexia that occurs in RA has not been addressed. Past research has shown resistance training in RA is associated with can decreased fat mass, and increased lean body mass, strength, physical function, and HRQL. Resistance training programs must be progressive in nature, and individually-tailored as pain, range of motion, and fatigue may all influence exercise involvement.

Chapter 3 - Methods

3.1 Overview of Study Design

This study was a randomized-controlled, pre-post pilot trial to evaluate recruitment rate, safety and acceptability of two exercise programs, and the feasibility of measurement methods and outcomes in preparation for a larger full-scale trial. We also explored the impact of 12 weeks of either progressive resistance + flexibility training (PRT+FLEX) or flexibility training (FLEX) on physical function and hypothesized mechanisms of change (i.e., metabolism, body composition, muscle strength). Eighteen sedentary adults with RA were randomly assigned to a PRT+FLEX or to a FLEX (control) group. PRT+FLEX consisted of two supervised resistance training workouts, and one home-based exercise session with resistance bands per week for 12 weeks. The PRT+FLEX group also completed the same flexibility exercises as the FLEX group following their program under supervision from the exercise supervisors. The FLEX group completed non-supervised flexibility exercises twice per week at home. All participants were asked to maintain their usual daily activity and diet throughout the study and to advise study staff of any concerns or change in RA status. Primary outcomes were changes in physical function (performance assessments and self-reported disability), while secondary outcomes were changes in metabolism, body composition, and muscle strength. Participants were tested at baseline and after completing the 12-week intervention.

3.2 Participants

Eighteen sedentary adults with stable RA were recruited from the Montreal area from January 2018 to May 2018. Inclusion criteria for this study included receiving care from a rheumatologist for RA, age 18-65 years, stable RA (i.e., no flares or changes in treatment in past three months) and currently sedentary (i.e., not meeting physical activity guidelines for past three months). Exclusion criteria included joint surgery within the past 6 months, pregnancy (currently or planned within 1 year), anabolic or nutritional supplementation, and pre-existing health issues that could cause cachexia (e.g., cancer). All participants received clearance to exercise from their treating rheumatologist (Appendix A). The McGill University Health Centers Ethics Board approved this research protocol (2018-3192), and all participants gave written informed consent prior to participation.

3.3 Recruitment

Participants were recruited from rheumatology clinics at the McGill University Health Centre and the greater Montreal area from January 2018 to May 2018. Flyers and advertisements were distributed in rheumatology waiting rooms, local arthritis clinics, pharmacies, and around the McGill campus describing the study and inviting participants to contact study staff. Participants were also recruited through arthritis and other patient/research groups in the using social media platforms such as Facebook, and research study groups in the Montreal area. Potentially eligible participants were told they would be either randomly assigned to a PRT+FLEX group or a FLEX group for 12-weeks.

3.4 Randomization Description

Participants were randomized to the PRT+FLEX group or the FLEX group using block randomization. The randomization strategy included three blocks of eight (four PRT+FLEX group and four FLEX group in each block) to keep the size of each treatment group similar. Exercise leaders placed the group assignments in sealed opaque envelopes.

3.5 Allocation

Results were placed in sealed opaque envelopes and envelopes were stored in a locked drawer. After baseline data was collected, participants were invited to select an available envelope. The number of envelopes available depended on the period in the block randomization. The exercise leaders provided the envelopes to participants, and participants were not told how many envelopes were left for each group. The exercise leaders were not blinded to the assignment of each participant.

3.6 Intervention Groups

3.6.1 Progressive Resistance Training + Flexibility Program (PRT+FLEX)

The PRT+FLEX group performed exercises using both free weights, and weight machines in combination with a home-based component that utilized resistance bands. The exercise program was tailored to the individual needs of each participant (i.e., intensity, difficulty), while also following the Canadian Society for Exercise Physiology (CSEP) guidelines (CSEP, 2006). Resistance exercises focused on training major muscle groups including the chest, upper back, shoulders, core, gluteals, quadriceps, and hamstrings using both free weights, and cable machines. Supervised progressive resistance training has been proven to be safe, effective, and sustainable in people with RA (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; Metsios & Lemmey, 2015).

Supervised PRT + FLEX (twice per week). After a baseline assessment at week 0, participants began a 12-week resistance exercise intervention consisting of two supervised exercise sessions (by A.S or N.C) at the McGill University Health Promotion Lab (MUHPL), and one home-based exercise session each week. The MUHPL has a range of exercise equipment including ellipticals, treadmills, weight machines (i.e., seated row, overhead pulldown, chest press, leg extension, leg curl, etc.) and free weights (dumbbells ranging from 2.5 lbs to 50 lbs). In the first two weeks of the study, to reduce muscle soreness, teach participants proper techniques, and allow participants to adapt to the training schedule, only two sets of 12 repetitions were performed. From weeks 3-12, the load was increased to challenge participants to complete six to eight repetitions for three sets (Lemmey et al., 2009). When more than the targeted repetitions were achieved, the weight was increased by an amount that allowed the targeted repetitions to be achieved. Training sessions were separated by at least two days of rest and the rest between sets was 1-2 minutes depending on the participant's preferences. An example of a supervised workout can be found in Appendix D. The beginning of every session included a 10-minute warm-up period that incorporated light aerobic exercise on an elliptical, stationary bicycle, or treadmill (depending on the participant's preferences). The resistance training section of the program lasted roughly 45 minutes, and consisted of four upper and four lower body activities that continually were rotated to enhance exercise adherence, excitement, and to expose the body to different stressors. The prescribed lower body exercises consisted of leg extension, leg curl, dumbbell squats, split squats, lunges, dumbbell step-ups and standing calf raises. The prescribed upper body exercises consisted of chest press, dumbbell bench press, chest flies, tricep extension, bicep curl, overhead pulldown, seated row, dumbbell row, and shoulder press. The weights used for each exercise were recorded for each set, and each workout to monitor participant progression (Appendix D).

To ensure consistency of the exercise program among participants, both leaders reviewed the structure of the program with Dr. Andersen on a regular basis and spoke with each other throughout the study to harmonize the training approach. Each participant was exposed to both exercise leaders (AS and NC) and other individuals (exercise science students) who supervised some sessions under the exercise leader's direction. At every session, participants were asked about their level of muscle soreness, and what exercises caused them pain or were difficult to perform. Adjustments to certain exercises were made by the exercise leaders if issues arose (i.e., elevating the heels to improve range of motion for a squat or holding a machine improved balance making it easier to perform a static lunge).

FLEX exercises. The end of each session concluded with participants stretching and the FLEX program. The FLEX exercises were designed to increase range of motion and followed exercise recommendations of The Arthritis Society and other arthritis groups. The FLEX program consisted of 8-10 flexibility exercises which were completed twice per week at each supervised exercise session (Appendix C). The FLEX exercises consisted of static, and dynamic stretches targeting large muscle groups including the hamstrings, quadriceps, shoulders, and exercises targeting smaller joints including ankles, and wrists.

Home program (once a week). Participants were also provided with a resistance training program to follow for their home-based routines which targeted major muscle groups (i.e., shoulders, chest, back, hamstrings, etc.). For the home-based exercise session, resistance exercises were performed using elastic resistance bands (Hygenic Corporation, Akron, OH, USA), which were given to participants by the exercise leaders. In the first session of the supervised program, participants were shown by exercise leaders how to correctly perform exercises, and execute variations in certain exercises. This was important to allow participants with painful joints or range of motion limitations to modify existing exercises and complete the workout. Participants were given the least stiff resistance bands (red = 1.8 kg) at baseline, and told to progress whenever they felt the exercises were too easy (i.e., to green bands – 2.3 kg or blue bands -3.2 kg). Participants were given a brochure of possible exercises (Appendix B) and asked to complete 6-8 exercises for 2-3 sets, and 10-12 repetitions. Participants were asked to maintain a training log indicating how many exercises, repetitions, and sets were completed in each workout. Training logs were reviewed by exercise supervisors throughout the program, and participant questions/comments were addressed during on-site sessions. If needed, exercises were modified at individual meetings to maintain interest and facilitate adherence to exercise. Additionally, as participants progressed through the home-based component, they had the option of changing resistance bands to increase the intensity of the resistance exercise.

3.6.2 Flexibility (FLEX) Group

Like Lemmey et al. (2009), we elected to have all control participants complete flexibility exercises as these are commonly prescribed for everyone with RA to improve joint flexibility. However, this type of exercise is not sufficient to increase muscle mass or strength (ACSM, 2013).

Participants in the FLEX group were given a flexibility exercise handout, and completed the same exercises described above twice per week at home (Appendix C). At the baseline visit, FLEX participants were taught how to safely stretch by exercise leaders, and showed variations in stretches if their joints were painful or range of motion was inhibited. FLEX participants met individually with their exercise supervisor for 20-30 minutes at weeks 6 and 12 to review progress and address any questions they had. They were asked to keep a diary of all FLEX sessions to monitor adherence and adverse effects.

3.7 Outcomes

3.7.1 Participant Characteristics

Participant (i.e., age, sex, education, employment, smoking status, co-morbidities), and

RA characteristics (i.e., duration) were obtained at baseline using a questionnaire (Appendix E). Participants also provided a list of all current arthritis medications, and were asked to inform study staff if there were any changes to their medications.

3.7.2 Anthropometric and Body Composition Assessment

Anthropometric measures were taken following standard procedures (ACSM, 2013). Height was measured to the nearest 0.1 cm with a wall mounted stadiometer, and weight to the nearest 0.1 kg on a medical scale (Seca, Hamburg, Germany). Waist, and hip circumference were measured to the nearest 0.5 cm following standard procedures (ACSM, 2013).

Body composition was assessed with dual energy x-ray absorptiometry (DXA) using a GE Lunar iDXA. The DXA was calibrated daily, and participants were positioned according to the manufacturer's recommendations and guidelines (GE Healthcare, Madison, WI, USA). Each total body scan provided an estimate of lean tissue mass, appendicular lean tissue mass, body fat percentage, visceral fat, and total bone density.

From the total body scans, appendicular lean mass index (ALMI - appendicular lean mass, kg/height^2), FMI (fat mass, kg/height^2), and FFMI (fat-free mass, kg/height^2) were all calculated. Additionally, a fat-adjusted appendicular lean mass index ($ALMI_{FMI}$) was calculated with reference values available for age, sex and ethnicity (ALMI Z-Score = Actual ALMI Z-Score – Predicted ALMI Z-Score * (1/SD)) (Weber et al., 2016). $ALMI_{FMI}$ compares participants to other individuals of a similar age, sex, race, and adiposity identifying participants with lower muscle mass than expected (Weber et al., 2016).

Rheumatoid Cachexia Definitions. Three definitions were used to identify people with RC. Weber et al. (2016) classified "Low fat-adjusted lean for age" as an $ALMI_{FMI}$ Z-score $\leq$ -1, while “Fat-adjusted sarcopenia” was classified as an $ALMI_{FMI}$ Z-score ≤ -2 (Weber et al., 2016). RC was also defined as a Z-score ≤ -2. Additionally, RC definitions proposed by Engvall et al. (2008) and Elkan et al. (2009) were also used. Engavll et al. (2008) defined RC as a FFMI below the 10^{th} percentile and a FMI above the 25^{th} percentile, while Elkan et al. (2009) defined RC as a FFMI below the 25^{th} and a FMI above the 50^{th} percentile.

3.7.3 Resting Energy Expenditure

REE was assessed via indirect calorimetry. Each assessment was conducted using a Sensormedics VmaxTM metabolic cart (Viasys, Conshohocken, PA, USA), and a ventilated canopy system using standardized methods (Wadden, Foster, Letizia, & Mullen, 1990). The cart was calibrated daily with all assessments performed in the morning (7- 10 a.m). Participants were instructed to fast for 12 hours, and to not exercise vigorously the day prior to testing. Participants were placed in a supine position and instructed to stay awake for the 30 minutes during which expired gases were collected. REE was calculated using the Weir Formula, and was also estimated using the Harris-Benedict equation.

3.7.4 RA Disease Activity

The Routine Assessment of Patient Index (RAPID3) provides information of patient’s self-reported disability, fatigue, and overall health. The RAPID3 contains the Multi-dimensional Health Assessment Questionnaire (i.e., a shorter version of the HAQ) and two additional questions about patient global estimates of disease status and pain (Pincus, Swearingen, & Wolfe, 1999). This questionnaire assesses physical function, pain and perceptions of RA disease activity with higher scores reflecting higher disease activity and impairment (Appendix F). Each of the first 10 questions are rated from 0 (without any difficulty) to 3 (unable to do), while sections 2 (pain) and 3 (patient global disease activity assessment) are scored from 0 to 10. The RAPID3 is highly correlated with other disease activity measures (Pincus et al., 2011).

RA disease activity was also assessed using the RA Flare Questionnaire total score (RA-FQ) (Bartlett et al., 2017). The RA-FQ is a self-report measure that asks five questions regarding pain, physical function, fatigue, stiffness, and participation in social activities (Appendix H). Each item is scored from 0 to 10, and the total score is a sum of the five items (minimum = 0, maximum = 50). Higher scores are more representative of higher disease activity (Bartlett et al., 2017). Bartlett et al. (2017) found in 1,000 people with RA from Canada, France, and the Netherlands that the RA-FQ had high test-retest reliability (ICC = 0.93), and responsiveness (moderate to large effect sizes = 0.82 – 1.95).

3.7.5 Physical Function Assessments

Physical function was assessed using a combination of self-reported disability (MDHAQ, PROMIS- Physical Function 4A, RA-FQ Physical Function Rating Scale) and performance measures (400 m walk test and Short Physical Performance Battery).

Self-Reported Physical Function Assessments

Multi-dimensional Health Assessment Questionnaire (MDHAQ). The MDHAQ is a shorter version of the HAQ that assesses functional status (Maska, Anderson, & Michaud, 2011; Pincus, 2007). The MDHAQ contains 10 questions that aim to assess difficulty in performing daily physical tasks such as getting in and out of bed, and turning faucets on and off (Appendix F). Each of the 10 questions are rated from 0 (without any difficulty) to 3 (unable to do). The cumulative total is the sum of all 10 questions divided by 3, with lower scores reflecting less disability (Maska et al., 2011; Pincus, 2007). In RA, the MDHAQ has been shown to be strongly correlated (i.e., r = .5 – 1.0) with disease activity (r = 0.51) (Maska et al., 2011).

Patient Reported Outcomes Measurement Information System – Physical Function 4a (PROMIS-PF 4a). The PROMIS-PF 4a is a section of the PROMIS which evaluates physical function (Bartlett et al., 2015) (Appendix G). Four questions are scored from 1-5, for a possible 20 total points, with higher scores equating to better physical function. The score is then transferred to a standardized T-score with a mean of 50, and a standard deviation of 10.

Physical function rating scale. The single item physical function rating scale of the RA-FQ was also used (Bartlett et al., 2017). This item asks participants to rate the difficulty completing physical activities such as walking, preparing meals, or dressing. The score ranges from 0 (No difficulty) to 10 (extreme difficulty) with higher values reflecting worse physical function.

Performance Measures of Physical Function

Short Physical Performance Battery (SPPB). The SPPB is a widely used measure of tasks that mimic daily actions including static balance, gait speed, and timed chair-raises (Guralnik et al., 1994; Ostir, Volpato, Fried, Chaves, & Guralnik, 2002). The SPPB has been shown to have high reliability with intraclass correlation coefficients (ICC) ranging from 0.88 to 0.92 (measures made 1 week apart), and 0.77 (range: 0.72– 0.79) for measures made 6 months apart (Ostir et al., 2002).

To assess balance, participants were asked to stand with their feet together (tandem), staggered (semi-tandem), and with one foot in front of the other. For each position, the tester demonstrated the task, and timed the participant for a maximum of 10 seconds or until they lost their balance (Guralnik et al., 1994). The balance test was scored out of 0 to 4, with higher scores reflecting higher lower extremity functioning. Participants were also asked to walk four metres. Time was recorded for each distance (in seconds), and converted to a score from 0 to 4, with higher scores reflecting better mobility. The ability to rise from a chair (termed chair stand) was also assessed. If participants could rise from a chair without the use of their arms, they were asked to sit and stand as quickly as possibly for five repetitions (Guralnik et al., 1994). Repeated chair stands were scored from 0 to 4 with higher scores reflecting better lower body functioning. Scores on each component were summed together (total 12) with higher scores reflecting better overall physical function.

400 M Walk Test. The 400 m walk test measures functional capacity and has been linked to mortality, and mobility limitations (Newman et al., 2006). Participants completed two laps on the McGill indoor 200-m track, and could rest when needed. Time was recorded when the person began the test, and stopped when they completed both laps. In a sample of 132 RA participants (45-84 years of age), slower walking speed was associated with older age, higher depression scores, higher reported fatigue and pain, and worse body composition (Lusa, Amigues, Kramer, Dam, & Giles, 2015).

3.7.6 Muscle Strength

Maximal isokinetic knee extensor strength was assessed using the Biodex System 4 computerized dynamometer (Biodex Corp., Shirley, New York). Other studies of RA participants have used similar dynamometers to assess maximal strength of knee extensors, and elbow flexors (Lemmey et al., 2009; Marcora et al., 2005). Knee extensor strength is a common assessment of physical function in daily activities, and has been shown to have an ICC of 0.97

(range: 0.92 - 0.99) in a clinical population (Ribeiro et al., 2015).

Concentric isokinetic knee flexion and extension was tested at 60°/sec for the right leg, which is a similar mode to muscle strength testing in previous RA research (Lemmey et al., 2009; Marcora et al., 2005). The participants were secured using shin, thigh, hip, and chest straps, while the lateral condyle of the femur was aligned with the input axis of the dynamometer as instructed by the Biodex User's Guide (Biodex Pro Manual, Applications/Operations. Biodex Medical Systems, Inc., Shirley, NY. 1998). Participants completed three maximal concentric-concentric isokinetic repetitions, rested for 2-minutes, and then completed a second set of three repetitions. Peak torque (muscle strength) for both extension, and flexion was averaged between the two sets.

3.7.7 Physical Activity

The International Physical Activity Questionnaire - Short Form (IPAQ-SF) was used to assess physical activity (Craig et al., 2003). The IPAQ-SF contains seven questions that assess 7-day activity across four different intensities (vigorous, moderate, walking, and sitting) (Appendix J) (P. H. Lee, Macfarlane, Lam, & Stewart, 2011). The longer IPAQ is the most widely used physical activity questionnaire in the world containing 31 items, while the shorter version is becoming more popular because of the minimal need for participants to recall many different tasks (P. H. Lee et al., 2011). In people with RA, the IPAQ-SF is moderately correlated with accelerometry counts (r = 0.407) (Meeus, Van Eupen, Willems, Kos, & Nijs, 2011; M Tierney, Fraser, & Kennedy, 2015). The values for metabolic equivalents (METs) were calculated through the questionnaire by multiplying each minute the participant self-reported walking, and engaging in moderate, and vigorous activity that week. The MET values used were 3.3 for walking, 4 for moderate activities, and 8 for vigorous activities (IPAQ, 2005).

3.7.8 Exercise Self-Efficacy

The Exercise Self-Efficacy Scale (ESES) contains six questions that assess how confident participants are they can exercise despite varying circumstances (i.e., work requirements, feeling tired, time constraints, etc.) (Dzewaltowski, 1989) (Appendix I). Each question is rated on a scale from 1 (Not Certain) to 10 (Very Certain) and the total score is the sum of all questions (range = 0 – 60). In RA, the ESES has an ICC of 0.59 (moderate reliability), and a Cronbach's alpha of 0.89 (high reliability) (Nessen, Demmelmaier, Nordgren, & Opava, 2015).

3.7.9 Exercise Enjoyment

The Physical Activity Enjoyment Scale (PACES) is a list of eight questions on a 1-7 scale that assess pleasure, fun, and satisfaction related to physical activity (Kendzierski & DeCarlo, 1991). The sum of all 8 responses are summed for a minimum of 8, and a maximum of 56, with higher scores representing more activity enjoyment (Appendix I). The PACES has been used in adults with physical limitations and has high reliability (Cronbach's alpha of 0.95), and high internal consistency (r = 0.51) (Murrock, Bekhet, & Zauszniewski, 2016).

3.7.10 Exercise Adherence

Attendance rates were calculated using the supervised and unsupervised (home-based resistance bands) training logs. Additionally, the training logs recorded the total amount of weight completed for each exercise, each set, and each workout, allowing for changes in training-specific programming to be identified (Appendix D).

3.8 Confidentiality

Each participant was identified by a unique number. Linking information was stored on a secure, password protected file. All data were entered in a secure study database stored on university servers behind a firewall and backed up daily. Where possible, data was transferred directly from laboratory instruments into secured online files. All data was double entered independently by two graduate students (NC and AS), then compared to ensure accuracy.

3.9 Statistical Plan

Variable distributions were examined and descriptive statistics were calculated for all participants and by group. Between group differences were assessed using independent t-tests, chi-square, and Fisher exact tests when appropriate. Repeated measures analysis of variance was used to compare change over time in the two groups in physical function, body composition, muscle strength and REE. All calculations were conducted using SPSS v23 and a $p \leq .05$ was used to identify statistically significant differences.

3.10 Sample Size

The target sample size was set at 20 participants as this was thought to be sufficient in providing useful information about the recruitment rates, the feasibility of the exercise training programs and assessing the benefits and challenges associated with using certain outcomes (i.e., self-report physical activity, SPPB, etc.) in this pilot study (Thabane et al., 2010). Further, other RA pilot studies have used similar sample sizes (Rall et al.1996, Marcora et al. 2005).

Chapter 4 - Results

4.1 Participant Characteristics

Forty-two participants were assessed for eligibility in this study. Twenty-two people (54%) declined participation for a variety of reasons. Thirteen individuals (32%) were unable to commit to the exercise program, 5 people (12%) stated the distance to the intervention site was too far, 2 (5%) were currently meeting physical activity guidelines, and 1 individual (2%) was not within the age criteria of the study. Nineteen participants underwent testing at baseline. One individual was administratively withdrawn from the study after baseline testing as their level of physical function was significantly impaired suggesting additional changes to the training program would have had to been made. Thus, 18 participants were randomized to either PRT+FLEX (n = 10) or FLEX (n = 8). The flow of participants through the study is depicted in Figure 1.

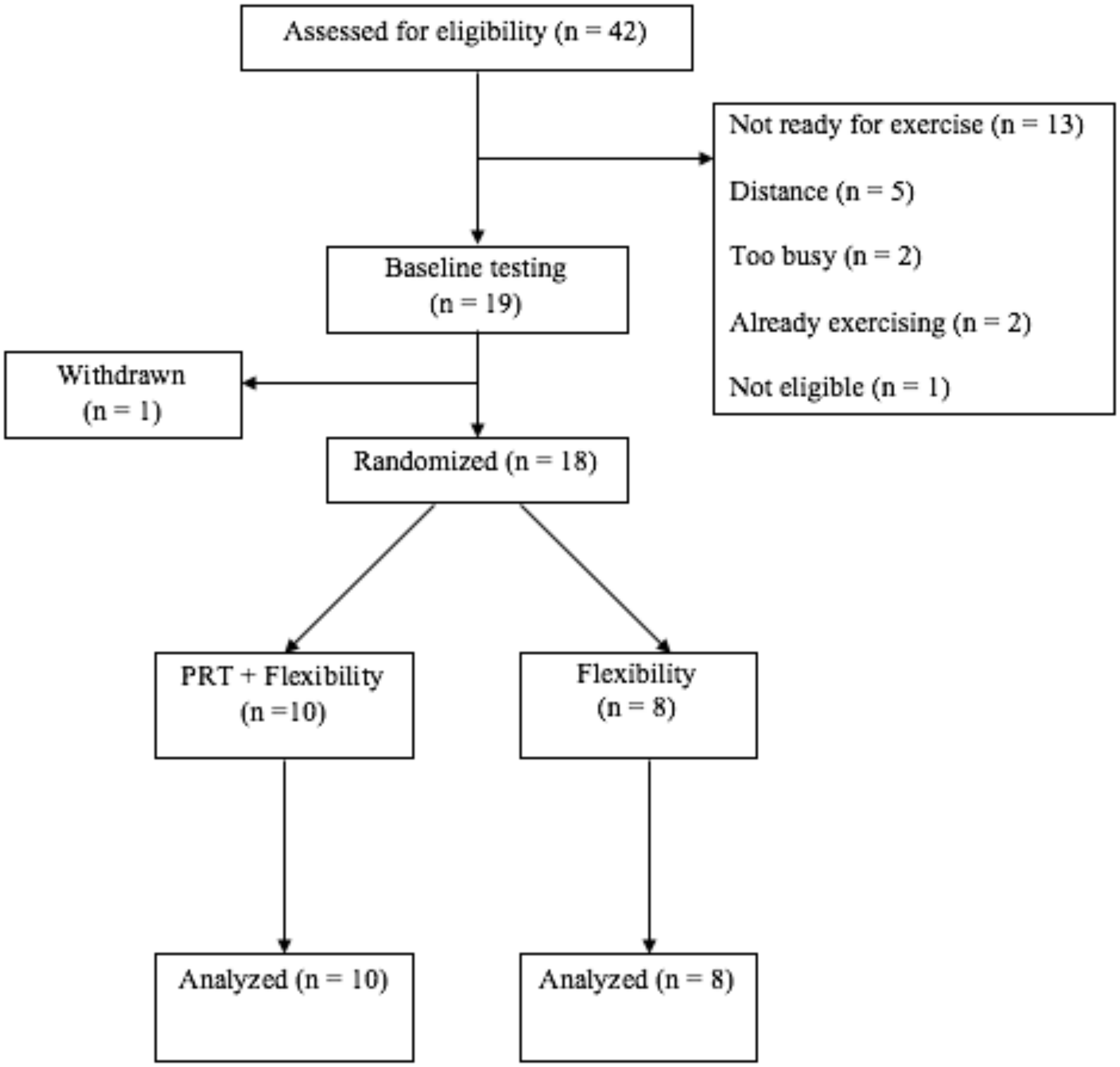

Figure 1. Flow chart describing participant recruitment, randomization, and follow-up through the study. PRT = progressive resistance training.

Participants were mostly female (94%), white (78%), well-educated (61% > high school education), and non-smoking (94%) (Table 1). There were no significant difference between groups at baseline except the flex group had a higher mean BMI. The one male participant was in the PRT+FLEX group. He was 63 years old, had higher MDHAQ scores (by 1.7), had a higher body fat percentage (by 3%) and was significantly heavier (~17 kg, $p = .05$) compared to all other participants. A sensitivity analysis was run removing this participant and comparing baseline characteristics, and the results were similar; the FLEX group continued to have a higher mean BMI even when the man was excluded.

Table 1. Baseline participant characteristics by group.

Mean (SD) or n (%)	**All Participants (*N* = 18)**	**PRT+FLEX (*n* = 10)**	**FLEX (*n* = 8)**	***p*-value**
Age (years)	38 (19)	33 (17)	43 (21)	.275
Female	17 (94%)	10 (100%)	7 (88%)	.444
Race				.249
White	14 (78%)	6 (60%)	8 (100%)	
Black	2 (11%)	2 (20%)	0	
Asian	1 (5%)	1 (10%)	0	
Other	1 (5%)	1 (10%)	0	
Education				.584
HS or less	7 (39%)	3 (30%)	4 (50%)	
Completed College	7 (39%)	4 (40%)	3 (37%)	
Post Graduate	4 (22%)	3 (30%)	1 (13%)	
Currently Smoking	1 (6%)	1 (10%)	0 (0%)	.357
Height (cm)	164.7 (7.6)	166.1 (8.0)	163.0 (7.2)	.411
Weight (kg)	65.1 (8.4)	61.7 (8.0)	68.3 (7.4)	.092
BMI (kg/m^2)	24.1 (3.1)	22.6 (2.1)	26.0 (3.3)	**.019**
BMI Categories				.154
Healthy (18.5-24.9)	13 (72%)	9 (90%)	4 (50%)	
Overweight (25-29.9)	4 (22%)	1 (10%)	3 (38%)	
Obese (> 30)	1 (6%)	0	1 (12%)	
RA Duration (years)	8 (5)	7 (5)	10 (6)	.348
RA Medications				.180
Biologics	5 (28%)	3 (30%)	2 (25%)	
csDMARDS	8 (44%)	4 (40%)	4 (50%)	
Corticosteroids*	3 (17%)	3 (30%)	0 (0%)	

* csDMARDS = conventional synthetic Disease Modifying Anti-Rheumatic Drugs

PRT+FLEX = Progressive resistance training with flexibility exercises group, FLEX = Flexibility group, BMI = Body Mass Index, RA = Rheumatoid arthritis.

4.2 Baseline Comparisons Between Groups

Body Composition. The two groups were similar in most body composition metrics however, there were some statistically significant baseline differences. The FLEX group had significantly more body fat (6.5 kg), visceral fat (719 g), had a higher body fat percentage (6.4%), and FMI (2.8 units) as compared to the PRT+FLEX group. The two groups had statistically similar amounts of total body lean mass, appendicular lean mass, lower body lean mass, and bone mass (Table 2).

Table 2. Baseline body composition measures by group.

Mean (SD) or n (%)	**PRT+FLEX (*n* = 10)**	**FLEX (*n* = 8)**	***p*-value**
Total Body Mass (kg)	61.66 (8.01)	68.26 (7.41)	.092
Lean Mass (kg)	39.96 (5.83)	40.08 (3.40)	.962
Fat Mass (kg)	19.39 (4.75)	25.93 (6.14)	**.021**
Bone Mass (kg)	2.30 (.37)	2.26 (.23)	.789
Appendicular Lean Mass (kg)	17.50 (2.72)	17.43 (1.33)	.950
Lower Body Lean Mass (kg)	13.40 (2.11)	13.28 (1.10)	.887
Visceral Fat (g)	222 (149)	939 (1028)	**.044**
Body Fat Percentage (%)	32.5 (5.8)	38.9 (6.0)	**.037**
Fat-Free Mass Index (kg/m^2)	15.23 (.92)	15.92 (.54)	.077
Fat-Mass Index (kg/m^2)	7.05 (1.85)	9.85 (2.71)	**.020**
Rheumatoid Cachexia			
Weber et al.	0	1 (13%)	.250
Engvall et al.	2 (20%)	1 (13%)	.671
Elkan et al.	2 (20%)	1 (13%)	.671

PRT+FLEX = Progressive resistance training with flexibility exercises group, FLEX = Flexibility group. Engvall Formula = FFMI below the 10th percentile FMI above the 25th percentile (Engvall et al., 2008). Elkan Formula = FFMI below the 25th and FMI above the 50th percentile (Elkan et al., 2009).

Rheumatoid cachexia. At baseline, depending on the definition used, up to three participants were identified as having RC. Using the Weber et al. (2016) formula, the one person classified as having RC was a white, 63-year old male, and had significantly more visceral adiposity (~2.7 kg, $p < .001$) than other participants. He also had more total fat (~8 kg), and similar amounts of appendicular lean mass compared to other people in the study. Additionally, he had a numerically but not statistically higher MDHAQ (1.6 vs. 3.3, $p = .196$), and RA-FQ total disease activity score (38 vs. 23; $p = .219$). Using the definitions of RC proposed by Engvall et al. (2008) (i.e., < 10th percentile in FFMI, and > the 25th percentile for FMI), and Elkan et al. (2009) (< 25th percentile for FFMI, and > 50th percentile for FMI), the same three participants were identified as having RC. Compared to non-cachectic participants, the three cachectic individuals were younger (34 (25) vs. 38 (18) years, $p = .725$), had a shorter disease duration (6 (4) vs. 9 (6) years, $p = .404$), while none of them were on csDMARDs or Biologics ($p = .090$ and $p = .239$ respectively). The same individual identified by the Weber et al. (2016) equation was also identified by the Engvall et al. (2008) and Elkan et al. (2009) equations.

Physical Function. Overall, at baseline, participants self-reported some level of initial disability (Table 3). The mean PROMIS Physical Function scores were 1 SD below the population norm indicating moderate disability; similarly, the MDHAQ scores (mean = 1.7 (1.3)) and RA-FQ Physical Function item (mean = 4.6 out of 10) both reflected moderate levels of disability. The mean SPPB for the group was 11.1 out of a possible 12, while the mean 400-m walk time was 292 (32) seconds. The group's knee extension and knee flexion strength were 84.5 (27.2) Nm, and 48.6 (9.8) Nm respectively.

Table 3. Baseline physical function, resting energy expenditure, and physical activity by group.

Mean (SD)	PRT+FLEX (*n* = 10)	FLEX (*n* = 8)	*p-value*
Self-Report Physical Function			
PROMIS Physical Function 4a*	40.3 (8.2)	41.1 (5.7)	.815
MDHAQ (0-3)†	1.6 (1.4)	1.9 (1.2)	.624
RAFQ–Physical Function (0-10)†	4.7 (2.1)	4.5 (2.4)	.853
Physical Performance Measures			
Short Performance Physical Battery	11.8 (.7)	10.9 (1.6)	.180
Balance Section	4.0 (0.0)	4.0 (0.0)	-
Walk Section	4.0 (0.0)	4.0 (0.0)	-
Chair Stand Section	3.8 (.7)	2.9 (1.6)	.180
400-m Walk Test (s)	300.7 (37.9)	280.4 (21.0)	.194
Knee Extension Strength (Nm)	88.5 (32.1)	79.5 (20.5)	.498
Knee Flexion Strength (Nm)	50.4 (10.9)	46.3 (8.5)	.395
Resting Energy Expenditure (kcal/day)	1293 (282)	1234 (173)	.617
International Physical Activity Questionnaire SF			
Metabolic Equivalents per day	1426 (1814)	1957 (1753)	.476
Days moderate-vigorously active/week	2.1 (3.3)	3.0 (3.1)	.563
Days walking/week	4.6 (2.5)	5.1 (2.4)	.650

*Higher values represent better physical function

†Higher values represent greater impairments in physical function

PRT+FLEX = Progressive resistance training with flexibility exercises group, FLEX = Flexibility group, PROMIS-Physical function 4a = Patient Reported Outcome Measurement Information System (Bartlett et al., 2015), MDHAQ = Multi-dimensional Health Assessment Questionnaire (Pincus et al., 1999), RAFQ = Rheumatoid Arthritis Flare Questionnaire (Bartlett et al., 2016), IPAQ = International Physical Activity Questionnaire (IPAQ, 2005), METs = Metabolic Equivalents, SPPB = Short Performance Physical Battery (Guralnik et al., 1994).

Compared to the PRT+FLEX group, the FLEX group had slightly higher PROMIS-4a and MDHAQ scores, walked 20 seconds faster in the 400-m test but had lower knee extension and knee flexion strength.

Resting Energy Expenditure. REE was not statistically different between the two groups however, both groups were below their estimated REE values using the Harris Benedict equation (PRT+FLEX group was 100kcal/day below, and FLEX group was nearly 300 kcal/day below).

Physical Activity. Surprisingly, despite meeting the criteria for being sedentary at enrollment, the mean METs level for the entire group classified them as having a high level of physical activity (mean score = 1625 (1752) METs). Additionally, the group spent 3 (3) days per week being moderately-vigorously active in bouts of 10 minutes or more, and 5 (2) days per week walking in bouts of 10 minutes or more. The FLEX group was categorized as “high” on the IPAQ (>1500 METs), while the PRT+FLEX group was categorized as “moderate” (>600 METs). The PRT+FLEX group also had slightly higher exercise self-efficacy while self-reporting lower physical activity enjoyment as compared to the FLEX group.

4.3 Post Intervention Comparisons by Group

Body Composition. As shown in Table 4, weight was stable in both groups over 12 weeks. In the PRT+FLEX group, there was a trend (p = .066) for fat mass to decrease (-.14 kg) but increase (1.02 kg) in the FLEX group; bone, lean mass and fat free mass were similar at week 12. Both groups increased the amount of appendicular lean mass over time (p = .028); there was a trend (p = .062) for the increase to be more than eight-fold higher in the PRT+FLEX group. Lower body lean mass also increased over time in both groups (p = .030); though increases were more than twice as high in the PRT+FLEX group, the group X time interaction was not statistically significant. The FLEX group had significantly more visceral fat at both time periods as compared to the PRT+FLEX group at both time periods. There were significant group and group X time effects where percent body fat decreased in the PRT+FLEX group while it increased modestly in the FLEX group. There was a significant group X time interaction for FMI where it decreased over time in the PRT+FLEX group and increased in the FLEX group.

Rheumatoid Cachexia. Using the definitions of Weber et al. (2016), one participant classified as having RC in the FLEX group was still classified as cachectic at the end of the program. This individual gained a small amount of lean tissue mass (+.17 kg vs. +.19 kg in non-cachetic individuals) but also gained 1.2 kg of fat vs. 0.4 kg gained by others without RC throughout the study. Using the Engvall et al. (2008) definition of RC, one person in the PRT+FLEX who was originally cachectic at baseline was no longer cachectic at follow-up. This individual was a 19-year old Asian female, who increased her lean tissue mass over 1.8 kg (vs. 0.08 kg) and gained less fat mass (0.17 kg vs. 0.46 kg) compared to other participants. With the Elkan et al. (2009) definition, one person was classified as RC in the PRT+FLEX group at follow-up who was originally classified as non-cachectic. This individual was a 64-year old black female, who lost nearly 1.53 kg of lean tissue mass (vs. +.30 kg) and gained .84 kg of fat mass (vs. .41 kg) compared to other individuals. Two participants identified at baseline to be cachectic by both the Engvall et al. (2008) and Elkan et al. (2009) definitions remained cachectic at follow-up. One of the participants was the individual identified in the Weber et al. (2016) calculation, while the other was a 20-year old white female who gained both lean tissue mass (.79 kg vs. .15 kg), and fat mass (.70 kg vs. .42 kg) compared to other participants.

Table 4. Body composition and rheumatoid cachexia classification before and after intervention.

Mean (SD)	PRT+FLEX n = 10			FLEX n = 8			*p-value*		
	Week 0	Week 12	Change	Week 0	Week 12	Change	Group	Time	Group X Time
Body Mass (kg)	62.05 (9.02)	62.49 (9.34)	.13 (2.08)	68.26 (7.42)	69.11 (8.31)	.85 (1.99)	.153	.217	.684
Fat Mass (kg)	20.06 (5.08)	19.91 (5.65)	-.14 (1.0)	25.93 (6.14)	26.94 (6.30)	1.02 (1.30)	.430	.155	**.066**
Bone Mass (kg)	2.21 (.36)	2.20 (.33)	.01 (.35)	2.26 (.23)	2.26 (.24)	.00 (.02)	.719	.551	.587
Lean Mass (kg)	39.77 (5.60)	40.38 (6.98)	.22 (1.42)	40.08 (3.40)	39.84 (3.46)	-.23 (1.20)	.965	.584	.229
Appendicular Lean Mass (kg)	17.39 (3.07)	18.18 (3.26)	.78 (.75)	17.43 (1.33)	17.50 (1.72)	.07 (0.65)	.800	**.028**	**.062**
Lower Body Lean Mass (kg)	13.60 (2.38)	13.96 (2.53)	.38 (.66)	13.28 (1.10)	13.45 (1.29)	.18 (.60)	.762	**.030**	.210
Visceral Fat (g)	216 (165)	274 (243)	58 (114)	938 (1028)	947 (988)	8 (86)	**.075**	.206	.339
Body Fat Percentage	33.40 (6.15)	32.83 (6.94)	-.58 (1.12)	38.88 (5.95)	39.93 (5.37)	1.05 (1.07)	**.058**	.402	**.010**
Fat-Free Mass Index (kg/m^2)	15.15 (1.02)	15.36 (1.08)	.21 (.53)	15.92 (.54)	15.84 (.73)	-.08 (.45)	.156	.604	.246
Fat Mass Index (kg/m^2)	7.32 (1.98)	7.27 (2.20)	-.05 (.35)	9.42 (2.64)	9.92 (2.81)	.50 (.41)	.153	**.041**	**.017**
Rheumatoid Cachexia									
Weber et al.	0	0	0	1	1	0	--	--	--
Engval et al.	2	1	-1	1	1	0	.736	0.334	0.334
Elkan et al.	2	3	1	1	1	0	.375	0.334	0.334

PRT+FLEX = Progressive resistance training with flexibility; FLEX = Flexibility.

Physical Function and REE

Self-Reported Physical Function. Group changes for self-reported physical function are shown in Table 5. After 12-weeks, clinically significant improvements were evident in both groups on the PROMIS – Physical Function (i.e., > 2 units, $p = .002$ for time). The PRT+FLEX group improved ~16% more than the FLEX group; there was a trend for the group X time interaction. At baseline, both groups were 1 SD below population norms; at follow-up, the PRT+FLEX group had improved to within the normal range.

Table 5. Changes in disability, performance, strength, and resting metabolic rate.

Assessment	PRT+FLEX n = 10			FLEX n = 8			*p-value*		
Mean (SD)	Baseline	Week 12	Change	Baseline	Week 12	Change	Group	Time	Group x Time
Self-Reported Disability									
PROMIS PF4a*	40.3	49.2	8.8	41.1	43.6	2.5	.434	**.002**	**.056**
	(8.2)	(7.0)	(2.5)	(5.7)	(6.4)	(4.1)			
MDHAQ †	1.6	0.6	-1.0	1.7	1.2	-.4	.366	**.005**	.300
	(1.4)	(0.5)	(1.3)	(1.1)	(0.8)	(0.6)			
RAFQ- PF †	4.7	1.0	-3.7	4.5	3.5	-1.0	.156	**.000**	**.002**
	(2.1)	(0.9)	(1.8)	(2.4)	(1.5)	(1.1)			
Performance									
SPPB Total	11.4	11.9	.5	10.9	10.9	.0	.186	.366	.366
	(1.3)	(0.3)	(1.4)	(1.2)	(1.6)	(0.5)			
Balance	4.0	4.0	.0	4.0	4.0		-	-	-
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	.0			
Gait (4m)	3.9	4.0	.1	4.0	4.0	(0.0)	.387	.387	.387
	(0.3)	(0.0)	(0.3)	(0.0)	(0.0)				
Chair-Stand	3.5	3.9	.2	2.9	2.9	.0	.148	.387	.387
	(1.1)	(0.3)	(0.7)	(1.7)	(1.6)	(0.5)			
400-m Walk (s)	300.7	241.6	-59.1	280.4	263.4	-17.0	.939	**.002**	**.051**
	(37.9)	(28.0)	(50.4)	(21.0)	(22.7)	(28.1)			
Strength									
KES (Nm)	94.2	120.8	26.6	79.5	86.5	7.0	.148	.113	**.342**
	(28.2)	(61.7)	(53.1)	(20.4)	(28.7)	(19.6)			
KFS (Nm)	52.3	71.0	18.7	46.3	58.6	12.3	.226	**.008**	.541
	(9.6)	(26.3)	(23.3)	(8.4)	(21.6)	(17.7)			
Resting Metabolic Rate									
REE (kcal/day)	1293	1442	144	1234	1400	165	.782	**.014**	.892
	(282)	(274)	(261)	(174)	(205)	(211)			

*Higher values represent better physical function
†Higher values represent greater impairments in physical function

PRT+FLEX = Progressive resistance training with flexibility exercises group, FLEX = Flexibility group, PROMIS-Physical function 4a = Patient Reported Outcome Measurement Information System (Bartlett et al., 2015), MDHAQ = Multi-dimensional Health Assessment Questionnaire (Pincus et al., 1999), Short Performance Physical Battery (Guralnik et al., 1994), KES = Knee extension strength, KFS = Knee flexion strength, REE = Resting energy expenditure.

Similarly, both groups reported statistically significant improvements in MDHAQ scores from baseline to follow-up; although the PRT+FLEX group had more than double the improvement of the FLEX group the group X time interaction was not significant. On the RA-FQ Physical Function item, there was a significant group X time interaction where the PRT+FLEX group reported about four times the improvement of the FLEX group.

Performance Measures. As shown in Table 5, the total score and component scores of the SPPB were similar at week 12. There was a significant group X time interaction for 400-m walk time; the PRT+FLEX group had clinically meaningful improvements (> 20 second difference), reducing baseline times by 20% whereas the FLEX group improved by 6%.

Knee extension strength did not significantly change over time. There was however, a significant effect of time ($p = .008$) for knee flexion strength with the PRT+FLEX group increasing flexion strength more than the FLEX group (36% compared to 27%) though the group X time interaction was not statistically significant. Figure 2 illustrates the increases in selected lower body exercises.

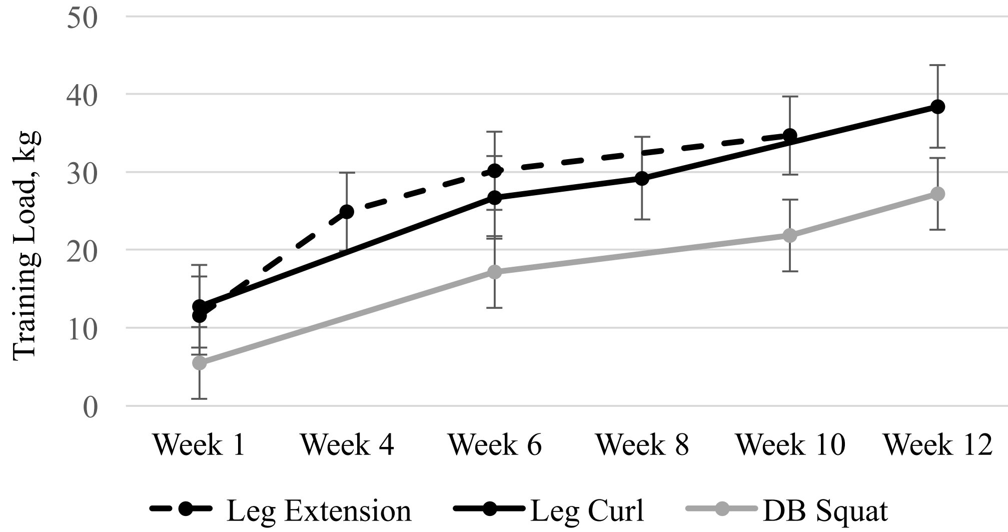

Figure 2. Increases in 8-repetition maximum for selected exercises for 8 RA participants during a 12-week resistance training program. Training load was determined by averaging the weight achieved for the last workout in each week. Data are presented as means ± SE.

Resting Energy Expenditure. As shown in Table 5, REE increased significantly in both groups by roughly 12%. At follow-up, REE had normalized in both groups as the PRT+FLEX group was 2% above predicted values, while the FLEX group was 6% below predicted values.

Adherence. Overall, adherence for the training program was high (88%). Mean adherence was 90% (9%) (range = 25 – 35 sessions) for the overall PRT+FLEX group and was 95% (7%) (range = 19 – 24 session) for the supervised exercise program, and 81% (19%) (range = 5-12 sessions) for the home-based component. In the FLEX program, participants self-reported 83% (12 %) (range = 15 -24 sessions) adherence.

Safety. No training related injuries were experienced through the study, and participants did not report any range of motion, joint pain, or muscle soreness issues.

Disease activity. As shown in Table 6, there was a significant group X time interaction for both the RAPID3 the RA-FQ total score suggesting that disease activity had improved in both groups from baseline to follow-up. Improvements were substantially larger in the PRT+FLEX group as compared to the FLEX group for both measures.

Exercise Enjoyment, Self- Efficacy, and Physical Activity. Both groups increased their physical activity enjoyment, exercise self-efficacy, and self-reported physical activity from baseline to follow-up as shown in Table 6. The was a significant group X time interaction where the PRT+FLEX group reported significantly higher exercise enjoyment scores (28%) than the FLEX group after the 12-week program. There were no significant effects of time, group, or group X time interactions for exercise self-efficacy, METs per day, days of moderate-vigorous activity per week (at least 10 minutes) or walk days per week (at least 10 minutes of walking).

Table 6. Changes in RA disease activity, exercise self-efficacy and confidence, and physical activity.

	PRT+FLEX n = 10			**FLEX n = 8**			***p-value***		
Mean (SD)	**Baseline**	**Week 12**	**Change**	**Baseline**	**Week 12**	**Change**	**Group**	**Time**	**Group x Time**
Disease Activity									
RA-FQ Total	25.4 (10.1)	8.5 (4.5)	-16.9 (8.7)	20.3 (12.0)	18.9 (10.0)	-1.4 (7.5)	.530	**.000**	**.002**
RAPID3	3.5 (1.6)	1.4 (0.9)	- 2.1 (1.3)	3.0 (1.8)	3.2 (1.6)	.2 (1.1)	.355	**.007**	**.002**
Exercise Self-efficacy and Confidence									
Exercise Self-Efficacy Scale	41.5 (12.9)	45.9 (9.2)	4.4 (7.8)	38.4 (14.9)	39.5 (12.8)	1.1 (7.2)	.420	.143	.374
Physical Activity Enjoyment Scale	41.1 (11.6)	52.8 (3.0)	11.7 (10.5)	44.3 (7.4)	43.0 (8.9)	-1.3 (11.0)	.314	**.067**	**.026**
Physical Activity									
METs per day	1425 (1818)	3951 (3201)	2525 (4014)	1957 (1753)	2657 (4558)	700 (4687)	.714	.172	.429
Moderate-vigorous (days)	2.1 (3.3)	5.1 (3.0)	3.0 (4.3)	3.0 (3.1)	2.75 (2.8)	-.3 (4.6)	.487	.201	.140
Walking (days)	4.6 (2.5	5.6 (2.1)	1.0 (3.1)	5.1 (2.4)	4.8 (2.5)	-.4 (1.6)	.867	.612	.272

PRT+FLEX = Progressive resistance training with flexibility exercises group, FLEX = Flexibility group, RA-FQ = Rheumatoid Arthritis Flare Questionnaire (Bartlett et al., 2016), RAPID3 (Bartlett et al., 2016), METs = Metabolic Equivalents.

Chapter 5 – Discussion, Conclusion, Recommendations

5.1 Discussion

The primary finding of this study is that in people with RA, 12 weeks of resistance exercise was safe and effective, and resulted in clinically meaningful improvements in physical function. At baseline, both groups reported similar levels of moderate physical disability. At follow-up, the improvements in physical function were two- to four- fold larger in the group doing both resistance training and flexibility as compared to the group doing only flexibility (i.e., range of motion) exercises. Additionally, by 12 weeks, physical function levels for individuals in the resistance training group were at the expected levels for the general US population on both the PROMIS-Physical Function 4a and the MDHAQ (Maska et al., 2011; Orbai & Bingham, 2015). Notably RA disease activity decreased in both groups, but significantly more in the group completing resistance training suggesting not only was exercise safe, but it appeared to reduce RA symptoms and disability. This is clinically meaningful, as disability is common in people with RA, and the societal and economic burden associated with RA-related disability continues to grow (Birnbaum et al., 2010). Disability greatly affects activities of daily living, and the ability to work and live independently. For example, up to 40% of participants report not being able to engage in valued life activities (Katz, 2005), and up to 39% reported work disability rates 10 years after diagnosis (Lindqvist, Saxne, Geborek, & Eberhardt, 2002).

These findings are in contrast to those of Lemmey et al. (2009) who in a similar study, assessed changes in disability in 28 people with RA who were randomly assigned to either 24-weeks of resistance training or to a range of motion program. At follow-up, no significant differences were evident on the MDHAQ between groups. A possible explanation for the differing results is that participants in this study were much younger (nearly 20 years), and had much higher mean baseline scores (1.7 vs 0.7) compared to the Lemmey et al. (2009) participants. To our knowledge, the PROMIS-Physical Function 4a, and RA-FQ Physical Function has not been used in RA resistance exercise studies to date, yet similar physical function assessments in other resistance training studies in RA parallel the findings of this study. Marcora et al. (2005) had ten people with RA complete a 12-week supervised resistance training program (3 times per week, 8 exercises completed in 3 sets of 8 repetitions) while 10 age-, and sex-matched RA individuals served as the control group (continued usual care). Participants in the resistance training group demonstrated greater changes in the advanced activities of daily living (ADL) scale compared to a control group (-.3 vs. -.1, $p < .008$). Importantly, the significant improvements in the ADL scale were similar to changes seen in physical performance tests such as the 30-second Sit-to-Stand test (4.4 vs. 0.6, for intervention vs. control, respectively; $p = .001$). Finally, Morsley et al. (2017) used the HAQ to track physical functioning after a 6-week high intensity resistance exercise program. Eighty-three RA individuals (mean age = 51 years, 60% female) completed a supervised group exercise program once a week consisting of 8-10 total-body exercises, for 8-12 repetitions. They reported clinically meaningful and statistically significant changes from baseline to follow-up (mean decrease in HAQ = -0.24, $p < .0001$). Hakkinen et al. (2001) also examined the effects of a two-year strength training program on muscle strength, physical function and disease activity in 62 RA participants. Participants were randomized to an exercise group (mean age = 49 years, 58% female, disease duration of ten years) or a range of motion control group (mean age = 49 years, 65% female, disease duration of eight years). The resistance training program was unsupervised and consisted of total-body exercises completed twice a week for two sets of 8-12 repetitions. They found significant between group differences after 18 (-0.24, $p < .01$), and 24 months (-0.22, $p < .05$) in the HAQ with the strength-training group improving more than the control group.

A meaningful improvement in the 400-m walk test (>20 seconds), a measure of functional capacity, was observed in the PRT+FLEX group as they were 59 seconds (20%) faster at follow-up compared to baseline (Kwon et al., 2009). The FLEX group almost achieved meaningful improvements in the 400-m walk time (17 seconds faster), but improved relatively by only 6% (time effect of $p = .002$, interaction effect of $p = .051$). This suggests that compared to the FLEX group, the PRT+FLEX group had improved mobility and lower body functioning. Longer duration walk tests may offer some advantages compared to shorter ones (Rolland et al., 2004) as they provide a more reliable indicator of sub-maximal exercise tolerance, and endurance than shorter walk tests (i.e., 4-m or 50-foot). Additionally, shorter tests may be influenced by factors other than muscle strength, or lower body functioning such as anaerobic capacity and muscle power (Graham, Ostir, Fisher, & Ottenbacher, 2008). Although this was the first RA-resistance training study to use the 400-m walk test, other studies have often used the 50-foot walk test. In a 12-week resistance training program that included eight RA individuals (mean age = 42 years, 63% female, disease duration of 15 years), Rall et al. (1996) reported significant improvements in participants' 50-foot walk times (-2.0 s; $p < .005$). Similarly, Flint-Wagner et al. (2009) and Lemmey et al. (2009) found reductions of 1.2 and 1.5 seconds respectively in 50-foot walk times after resistance training programs of 16, and 24 weeks whereas the control groups' times stayed relatively similar (+.8 seconds and -.5 seconds respectively). Taken together, these results align with the findings of Rall et al. (1996), Hakkinen et al. (2001), Marcora et al. (2005), Flint-Wagner et al. (2009), Lemmey et al. (2009), and

Morsley et al. (2017) suggesting resistance training is associated with meaningful improvements in both self-reported and performance measures of physical function in people with RA.

It was also hypothesized that the PRT+FLEX intervention would be associated with improved body composition (increased appendicular lean mass and lower body fat), increased muscle strength, and normalization of REE. There was a significant group by time interaction for body fat percentage and FMI, as both measures decreased in the PRT+FLEX group but increased in the FLEX group ($p = .010$ and $p = .017$ respectively). Additionally, total fat mass and appendicular lean mass were trending towards significance (between group differences of $p = .066$ and $p = .062$ respectively) with greater improvements being in the PRT+FLEX group. As body composition is a health concern in RA, finding new ways to simultaneously decrease fat mass and increase lean tissue may have important long-term health implications and represent a public health priority. A 2018 study utilizing data from over 50,000 health professionals followed for 21 years reported that those in the highest quintile of fat mass had a 35% higher chance of mortality compared to those in the lowest quintile (Lee et al., 2018). Individuals with RA also have lower lean tissue mass compared to healthy age, and sex-matched controls (Baker, Von Feldt, et al., 2014), and importantly, lean tissue mass is inversely associated with disability in RA (Giles et al., 2008; Kramer et al., 2012). Marcora et al. (2005) reported a reduction in body fat percentage in participants completing resistance training as compared to the control group (-0.9% vs. +0.2%, $p = .047$). In contrast, Rall et al. (1996) reported no change in total body fat mass with resistance exercise. A possible explanation for this is that the PRT program in this study more closely matched the training volume prescribed by Marcora et al. (2005) where participants exercised an average of 2.5 times per week at similar training intensities. The Rall et al. (1996) study prescribed resistance training only twice per week, which may not have been sufficient enough to induce body composition changes. In contrast to Marcora et al. (2005), there were no significant changes in total lean mass (p = .229), appendicular lean mass (p = .066), or lower body lean mass (p = .210) as a result of resistance training, although the PRT+FLEX group had greater improvements compared to the FLEX group in each measure. Although the Marcora et al. (2005) program was comparable to this study in terms of duration and number of participants (i.e., 12-weeks, N = 20), their exercise group included 4 males (40%) whereas our resistance training group was all females. Muscular adaptation to resistance exercise is likely to differ between men and women where men accrue muscle mass more readily (Burd, Tang, Moore, & Phillips, 2009).

Only a few individuals were classified as having RC at the start of the study. This is in contrast to the only other resistance study to classify RC in people with RA (Lemmey et al., 2009). Lemmey et al. (2009) found that after 24-weeks, five participants in the resistance training group who were previously classified as cachectic were non-cachectic at follow-up, while the seven cachectic individuals identified at baseline in the control group remained unchanged after 24-weeks. There are several possible explanations as to why differences were seen between the two studies. First, the mean age of participants in Lemmey et al.'s (2009) study was 58 years, over 20 years older than the sample which could impact the progression of RC. The Lemmey et al. (2009) study was also 24 weeks in duration, twice the length of this intervention which allowed more time for body composition to change in more participants and to a greater degree. Lemmey et al. (2009) also used different criteria to identify cachexia, and had different thresholds compared to Webber et al. (2016), Engvall et al. (2008), and Elkan et al. (2009).

Muscle strength, as measured by knee extension and knee flexion improved 20% and 10% more for each, respectively, in the PRT+FLEX group as compared to the FLEX group (differences were not statistically different between groups). Muscle strength increases in relation to increasing duration and intensity of training (Flint-Wagner et al., 2009; Rall, Meydani, et al., 1996). It is notable that previous research used repetition of the actual exercises to measure strength whereas the training program for this study utilized motions that were non-repetitive to measure strength at baseline and follow-up (i.e., knee extension and knee flexion motions). Rall et al. (1996) report that after 12-weeks of high-intensity resistance training, RA participants increased strength by 57% increases ($p < .0005$), which is similar to the 46% increase in 3-RM ($p < .01$) found by Flint-Wagner et al. (2009) after 16-weeks of resistance training. These studies both had participants perform similar exercises 2-3 times per week for the duration of the training program. Thus, the reported changes in strength may be more attributed to the neuromuscular adaptations of training rather than true increases in strength (Campos et al., 2002). To adjust for the confounding effects of familiarity with movements after repetitive practice, strength should be assessed using other methods (i.e., dynamometers). For example, Lemmey et al. (2009) measured knee extensor strength using an isokinetic dynamometer and reported a 25% improvement after a 24-week resistance program compared to a 7% increase in the control group. This is in line with this study's findings as the PRT+FLEX group increased 28% in knee extensor strength after the 12-week study, while the control group increased by less than a third of that (9%).

Participants completed an additional strength training session at home each week and were provided with different bands that allowed them to increase the intensity of the exercise. Although participants reported high adherence with the home-based exercises (81%), it is possible that the intensity of the home resistance training practice was less than that achieved during the supervised sessions. In one study that compared the effects of group and home-based low-impact aerobic exercise on fatigue, pain and mental health in RA, home exercisers performed less intense exercise than supervised exercisers, despite being told to work out at the same intensities (72% of supervised participants exercised at 60% of their maximal heart rate while only 45% of the unsupervised group did) (Neuberger et al., 2007). An important strength of the study was that participants were exposed to different ways of performing resistance activities which also offered opportunities to continue exercising at home once the program was completed. Completing home-based resistance band exercises also may help improve adherence to exercise once supervised programs end.

At baseline, participants were not in a hypermetabolic state as has been reported by others (Binymin et al., 2011; Hugo et al., 2016). The changes in REE resulting from a 12-week exercise program were similar to those reported by Rall et al. (1996) even though participants in this study exercised at a higher intensity and volume. In this study, after 12 weeks, REE had increased in both groups to predicted levels (PRT+FLEX group was 2% above predicted values, while the FLEX group was 6% below predicted values).

An interesting finding was that exercise enjoyment was significantly higher in the PRT+FLEX group compared to the FLEX group after 12 weeks (52.8 vs 43.0 out of 56), despite being 10% lower at baseline. A similar trend was seen with exercise self-efficacy (i.e., confidence to exercise despite of busy schedules, fatigue, responsibilities, etc.). Reduced exercise enjoyment and low exercise self-efficacy are both well-recognized barriers to exercise in people with RA (Cooney, Law, Matschke, Lemmey, Moore, Ahmad, & Thom, 2011; van Zanten et al., 2015). Both measure are important because they facilitate long term adherence to exercise, and are associated with longer duration and higher intensity levels of activity (Faghri, Chin, & Huedo-Medina, 2015). In a 3-month controlled, non-randomized group exercise study of 102 primary care patients completing group exercise vs. usual care (mean age = 50 years, 83% female, mean BMI of 30 kg/m^2), exercise enjoyment was 25% higher in the exercising group at 12-month follow-up (Hagberg, Lindahl, Nyberg, & Hellénius, 2009). Interestingly, it was also found that the PRT+FLEX group reported 23% greater physical activity enjoyment at follow-up compared to the FLEX group. Thus, it appears that even relatively short exercise interventions can substantially increase these two important aspects and ultimately impact long-term adherence to exercise.

Importantly, high retention and exercise adherence rates for both groups were observed in this study. The supervised program had higher adherence (95%) than many previous RA resistance studies which ranged between 73% – 85% (Flint-Wagner et al., 2009; Lemmey et al., 2009; Marcora, Lemmey, & Maddison, 2005). Adherence to the home-based program was 81%, which was also higher than the only other study with a home component (73%) (Häkkinen, Sokka, Kotaniemi, & Hannonen, 2001). One reason for this may be the close relationships study participants reported with exercise supervisors which may have contributed to exercise enjoyment. Supportive relationships can be facilitated by routinely asking participants about their muscle soreness or if they are experiencing pain or discomfort following workouts. Modifying exercises that were too painful or could not be performed due to range of motion limitations also may have contributed to both adherence and exercise enjoyment. For example, for participants that had trouble squatting, putting a stability ball between their back and a wall allowed for a deeper range of motion to be achieved. Furthermore, for those participants who had sore wrists, training gloves were given to minimize the stress imposed on the wrist joint.

Focus group studies in people with RA suggest that while not everyone reports enjoying exercising, it was individual expectations of outcomes associated with exercise that influenced whether they were active or not (Kibblewhite, Hegarty, Stebbings, & Treharne, 2017). Providing non-exercisers with positive experiences may offer important opportunities to encourage sedentary people to become active. While it was not specifically asked what aspects of the program participants enjoyed, it is likely that the social (i.e., interacting with exercise coordinators), psychological (i.e., changes in body perceptions) or emotional (i.e., changes in feelings of anxiety) benefits of exercise play important roles. This also holds important implications for personal trainers or exercise specialists working with people with RA. Developing a personal relationship with participants and keeping an open dialogue about how they are feeling throughout the program is important in influencing not only exercise enjoyment and efficacy, but long-term adherence.

One goal of this pilot study was to evaluate the feasibility and utility of outcome measures. While most measures performed as expected, self-reported physical activity may be problematic. For example, although participants were required to be physically inactive at baseline, most participants self-reported meeting moderate to high levels of physical activity guidelines on the self-report questionnaires. One reason for this may be that participants overestimated how active they were when assessed by the IPAQ. In future studies, it is recommended that objective assessments, such as accelerometry, be used to assess potential changes in physical activity. A second goal was to evaluate the potential rate of recruitment into the study. It was difficult to attract participants to the study as many commented that they were not ready to commit to the study or that the distance to the intervention site was too far. Additionally, some potential participants may have been skeptical about resistance training's efficacy for people with RA, and may have thought that exercise would exacerbate pre-existing conditions. For healthcare practitioners and exercise specialists, outlining the benefits of resistance training may prove to be important in attracting people with RA to future exercise studies.

5.2 Implications

The results of this study are useful for healthcare practitioners, exercise specialists, and people with RA. Specifically, these results contribute to the growing body of evidence that suggests resistance training can improve body composition and physical function in people with RA. Twelve weeks of resistance training was feasible, safe and effective in reducing disability, and not exacerbating disease activity. High adherence rates were observed, and the resistance training and flexibility programs appear to be safe and feasible to test in a large, fully powered study. However, even these preliminary results offer new information and support for exercise specialists or healthcare professionals who may be hesitant to prescribe resistance exercise to people with RA. These results emphasize the importance of creating exercise programs that are tailored to individuals, flexible in approach, and allow for adjustment to be made depending on how active RA is on days when they exercise.

One of the major barriers to resistance training is a lack of knowledge or familiarity with safe and correct exercise resistance training techniques. Unlike aerobic exercises such as walking, running, or cycling, resistance training requires the use of weight machines, free-weights, and/or resistance bands that many people are not familiar with. Before individuals with RA begin a resistance program, it is critical they receive medical clearance from their treating rheumatologist, and trainers should be aware of specific limitations or exercises to avoid. It is important for exercise specialists to carefully demonstrate how to correctly and safely complete all exercises. Additionally, resistance programs should be progressive in nature as incremental steps will challenge individuals in a safe way without overloading them or putting them through inappropriate intensities. Teaching participants how intense exercise should feel may increase exercise efficacy and maximize gains. Finally, designing exercise programs that are flexible and continue to evolve may keep interest high and importantly, increase exercise enjoyment which may promote long-term adherence.

One way to help ensure participants continue to exercise is to equip them with a variety of exercises to increase interest and offer options to be active even if they are feeling sore, fatigued, or are in pain. In this study for example, for participants with a restricted range of motion through the lower body, elevating their heels with a small plate (2.4 kg) while squatting allowed them to achieve a deeper range of motion. Additionally, for individuals who had issues holding dumbbells due to sore or damaged joints in the hands and wrist, machines that targeted similar muscle groups were used (i.e., chest press instead of dumbbell press). Exercise specialists are ideally suited to develop flexible programs for people with RA and help them progress through programs in a safe manner.

The feedback received from participants expressing how the resistance training program influenced their lives (e.g., feeling more confident in their bodies and in their ability to exercise, the value of making time for exercise,), was overwhelmingly positive and speaks to both the physical and psychological benefits regular exercise can confer. The results of this study suggest that disability, one of the most debilitating symptoms of RA, can be safely and effectively reduced through resistance training. Physiotherapists, exercise specialists, and healthcare practitioners should continue to support the introduction and prescription of resistance training whenever possible.

5.3 Strengths

A strength of this study was the high rates of adherence to completing both the supervised and home-based programs. Adherence was high in this study perhaps in part because of a variety of options (i.e., machines and exercise choices) and changed the program every few weeks by modifying or adding exercises, as needed. The exercise supervisors reported that strong relationships quickly developed with participants. Another strength of the study was the use of highly precise and reliable measures to assess body composition and energy metabolism to explore mechanisms leading to improvements in physical function. The exercise program followed RA-specific recommendations for exercise by providing a progressive, participant-specific program that was supervised by individuals specifically trained to work with people with arthritis (Metsios & Lemmey, 2015). This may have helped increase the safety (i.e., no injuries or adverse events) and enjoyment of exercise, and speaks to the benefit of combining supervised sessions with home practice.

5.4 Limitations

As this was a pilot study designed specifically to gather preliminary data for a larger, fully powered study, the goal was to evaluate the rate of recruitment, and appropriateness of study methods and outcome measures. Hence, this study was not optimally powered to compare outcomes. All changes were in the hypothesized directions, and it is likely that an adequately powered trial would demonstrate meaningful changes in many aspects of body composition and physical function. Recruitment was slower than expected (i.e., 3 participants/month); additional methods will be needed to attract and enroll large numbers of participants over briefer intervals. Participants were mostly female which means that the results may not generalize to men. Physical activity was assessed using self-report questionnaires which participants had difficulty providing reliable and valid information. Future studies should include objective assessments of physical activity and sedentary behaviours. Although all participants were asked not to change their diet, this was not monitored during the 12 weeks of the study. Diet may play a role in changing body composition and should be examined by food scientists in future investigations.

5.5 Future Directions

Based on the findings of this study, the following recommendations are:

1) Larger, adequately powered resistance training trials in RA should be conducted to identify possible sex differences in response to resistance training.
2) Future studies could examine the possible effects of resistance training on other lifestyle behaviours such as physical activity, diet, smoking status, and sleep patterns. As exercise levels increase, there may be an inclination to improve daily life habits. When possible, lifestyle outcomes should be measured objectively (i.e., accelerometers to measure physical activity) to reduce the possible bias that exists in self-report.
3) Future programs could explore the effects of resistance training programs on preventing disability and rheumatoid cachexia.
4) Augmenting resistance training with dietary or nutritional supplementation (i.e., high protein diets or creatine) may enhance the effects of exercise. Future studies should explore these potential synergistic effects.
5) The role of exercise in altering energy metabolism is still relatively unknown in individuals with RA. Longer duration resistance training interventions (i.e., more than 12 weeks) that monitor and account for RA disease activity are needed to better understand the complex relationships among RA, inflammation, and rheumatoid cachexia.

5.6 Conclusion

Within the delimitations and limitations of this project the following conclusions are:

1) A 12-week tailored RA-specific progressive resistance exercise program was safe (i.e., did not result in any injuries or adverse events) and enjoyable.
2) A resistance-training program can effectively improve both self-reported disability and physical performance in RA. This was shown by the improvements we observed on both self-reported disability (PROMIS- Physical Function 4a, MDHAQ, RA-FQ – Physical Function) and performance tests along with clinically meaningful changes in the 400-m walk test. Importantly, the PRT+FLEX group had larger improvements compared to the FLEX group in all subjective and performance-based physical function assessments.
3) A 12-week resistance-training program may also decrease body fat illustrated by the significant reductions in body fat percentage and FMI. This is important as altered body composition has a significant influence on physical function and to the development of comorbidities.
4) The resistance program also led to specific and objective increases in muscle strength as measured by knee extension and knee flexion. Although both groups improved, the PRT+FLEX group demonstrated greater changes in strength than the FLEX group. REE was not significantly changed by the resistance training program, although values were more normalized for all participants at follow-up.
5) Importantly, the 12-week resistance training program had positive effects on participant exercise enjoyment. The results from the PACES questionnaire illustrated a significant change between the two groups over the 12-weeks, with the PRT+FLEX group

increasing their exercise enjoyment by nearly 30%. This could have important implications for the long-term adoption of a more active lifestyle.

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Appendices

Appendix A: Physician Letter

Centre universitaire de santé McGill
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Les meilleurs soins pour la vie
The Best Care for Life

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Fax: (514) 843-1493

Dear Doctor:

Your RA patient, ______________________, has expressed an interest in participating in our randomized controlled study. Our goal is to better understand how exercise affects **rheumatoid cachexia and hypermetabolism, along with improving physical function and wellbeing**. In this RCT, we are comparing two exercise programs for people with RA: 1) a combined progressive resistance training and flexibility program; OR 2) flexibility training. Patients randomized to strength training + flexibility will complete two sessions at a private McGill exercise research facility under the supervision of graduate students in kinesiology, and one home practice using resistance therapy bands. Participants in the flexibility program will receive training in flexibility exercises to practice twice weekly at home. Both exercise programs last 12 weeks, have been specifically designed for sedentary individuals with RA, and are consistent with recommendations of The Arthritis Society, the Canadian Physical Activity Guidelines, American College of Sports Medicine, and others. Your patient must have stable RA to participate in this trial; we ask that, when possible, medication changes be made after their participation in the study has ended.

The exercise programs have been developed by Professor Ross Andersen, an exercise physiologist with experience developing programs for RA. All exercise is individually tailored based on initial testing results (metabolism, body composition, flexibility, strength, and endurance testing), additional recommendations you provide, and the preferences of your patient. Both programs start slowly and build up gradually.

In order for your patient to participate, we ask that you sign the letter indicating that you are aware your patient will participate in the study. **This form should be faxed to (514) 843-1493 or emailed to susan.bartlett@mcgill.ca.** Please let us know of any exercise limitation or restrictions your patient has so their program can be adapted as needed. The study investigators are available to answer any questions you may have about the study.

Best regards,

Susan J. Bartlett, PhD
Associate Professor of Medicine

This is to acknowledge that I am aware that my patient, ______________, wishes to participate in the RA Body Comp Study and recommend the following:
__ Unrestricted physical activity consistent with current recommendations for people with RA
__ Physical activity with particular attention to/avoidance of the following:
____
____

Name (print):____________________ Signature:________________ Date:_______________________

Appendix B: Exercise Resistance Band Information Sheet

Resistance Bands for Muscle Strength

Resistance training can increase muscle strength, maintain physical function, joint flexibility, and reduce joint pain. Strength training with resistance bands has unique benefits because the bands are inexpensive, portable, and simple to use. Resistance band training can work multiple muscles and joints at one time and in more than one plane which can improve function for daily activities.

Resistance Bands Exercise Guidelines

- Please follow the series of exercises recommended by your exercise consultant for your home practice. The following pages show how to perform different strength exercises using the elastic resistance bands that have been provided.
- Posture and body alignment are very important: keep your shoulders back and relaxed; tighten or "engage" your stomach muscles; keep your knees slightly bent; hold your wrists straight keeping your hand in line with the forearm.
- Perform all exercises with a slow, controlled pace (about 3 seconds to extend and 3 seconds to return).
- It is important to breathe while performing the exercises. Do not hold your breath – breathe out while your muscle is working and breathe in when it relaxes.
- The color of a band indicates resistance level. The progression from least resistance to greatest for a Thera-Band® is: red, green, and blue.
- Start with one set of 8 to 10 repetitions of each exercise. The muscle group you are exercising should feel fatigued at the end of each set. Gradually increase the number of repetitions to 12 to 16.
- If time allows; 2 to 3 sets of an exercise can be performed. Rest 30 seconds between sets.
- Progress to the next level of resistance (next color of band) when you are able to easily complete a set of repetitions.
- Muscle soreness may be experienced for 1 to 2 days after an exercise session. If pain persists for more than 3 or 4 days, do not exercise; please call us or tell us at your next exercise session.

Resistance Bands Strength Training Information and References

- Elastic Resistance Training (ERT) has been in use for almost a century.

Originally, banks were used by rehabilitation professionals to help their clients regain strength after an injury.

- Resistance increases as the band is stretched. The various color bands have the following resistance in pounds:

  Red: 3.9 lb
  Green: 5 lb
  Blue: 7.1 lb

- Store bands at room temperature in a box or a dark area. Do not store in direct sunlight.

Upper Body

Shoulders and Rotator Cuff

Front Raise

Stand with one or both feet on the band, shoulder width apart. Grasp the ends of the band with your palms facing each other. Raise your arms forward to about shoulder height, lower and repeat.

Lateral Raise

Stand with one or both feet on the band, shoulder width apart. Grasp the ends of the band with your palms facing down. Raise your arms out to your sides to shoulder height, lower and repeat.

Rotator Cuff

Stand with one or both feet on the band, shoulder width apart. Grasp the ends of the band with your palms facing down. Cross the band at your knees while extending your arms slightly forward. Raise your arms up no further than shoulder height and slightly wider than shoulder width; lower and repeat.

Bicep Curl

Stand with one or both feet on the band, shoulder width apart. Grasp the ends of the band with your palms facing forward and your arms held in close to the side of the body. Bending at the elbow, bring the hands up to shoulder height; lower and repeat.

Triceps

Stand with one foot extended forward placed on one end of the band with the length of the band on the inside of the leg. Lean forward and rest your hand on the extended knee to provide support for the lower back. Be sure your stomach muscles are engaged. Grasp the band about mid-thigh height with the opposite hand and keeping your arm close to your side, extend the shoulder rearward until the upper arm is parallel with the floor, the elbow is flexed, and the palm is facing the body. Keep the upper arm stationary and extend from the elbow backward. Flex the elbow and repeat.

Wrists

Extend lower arms in front of you. Your hands should be about shoulder width apart. Start in the "thumbs up" position and turn at the wrist so that your palms are facing up. Repeat the movement.

Upper Back and Chest

Upper Back

With arms outstretched and a slight bend in your elbows, grasp the band with your palms facing down at shoulder height. Your arms should be a little more than shoulder width apart. Extend arms out and bring the band towards your body. Return and repeat.

Lateral Pull Down

Stretch arms upward and forward with a slight bend in your elbow, grasping the band a little more than shoulder width apart. Keep your palms facing down. Extend your arms out and bring the band down towards your body to below chest height. Return and repeat.

Side Bend

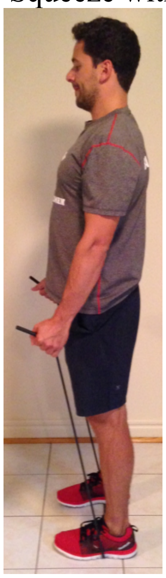
Stand on one end of the band. Grasping the other end of the band, extend your arm up on the side of your body. Bend to the side away from the band. Return and repeat. Repeat on the other side of your body.

Lower Body

Hips, Bottom, Thighs and Knees

Squats

This exercise can be done with or without the band. Stand on the band with feet shoulder width apart. Bend knees and sit back, making sure knees are behind toes. Extend your arms forward for balance.
Squeeze with the muscles in the bottom as you return to standing.



Parallel Leg Lifts

Sit on the front edge of a chair with one leg bent at a 90° angle and your other leg extended parallel to the floor. Flex your ankle and lift the extended leg while maintaining good form. Lower leg and repeat. Repeat exercise with your other leg. Return to the first leg and lift with the leg turned out, leading with the heel to strengthen the inner thigh. Repeat with the other leg.

Hip Flexion

Sit on the front edge of a chair. Place the band on the floor in front and place one foot on the band while holding both ends. Place the other foot in front of the band. Take the end that is next to your foot on the band and bring it in front of that leg and cross it over your opposite leg. Pull on both ends of the band so that it is tightly crossed over your leg. Lift and lower the leg with the band crossed over it. Repeat on the other side.

Calves, Ankles and Feet

Calf Raise

This exercise is done without the band. Use a chair for balance. Standing on one leg at a time, shift your weight to the ball of your foot while maintaining good posture. Return heel to the floor and repeat. Repeat with other leg.

Appendix C: Flexibility Program

Guidelines for ROM Exercises

To begin, include basic movements outlined in this brochure 2-3 times per week, for 10-15 minutes each session

As you become more comfortable with basic range of motion exercises, you can continue towards more advanced stretches

These include dynamic (movement) stretches (such as lunges), Thai Chi, and yoga

These exercises can still be done 2-3 times per week, at your personal preference. Complete each exercise 3 to 10 times

BENEFITS FROM EXERCISES

- Reduces stiffness
- Reduces pain
- Improves muscle strength
- Improves joints flexible
- Improves circulation

Guidelines for ROM Exercises

If you are unsure how to do the stretches in this handout, please let us know. We can help you get started.

Only Do the Exercises You Are Able To Do

- Make sure that you do not do push it any of the stretches
- The stretches are gentle. If they hurt you may be pushing too far
- If you have any questions do not hesitate to contact us!

Maintain Stable and Proper posture for Each Stretch

- Do not bend your joints to push the stretch further
- Avoid rounding your shoulders

Keep Each Movement Slow and Controlled

- Hold for 15 to 30 seconds

Do NOT Hold Your Breath

Keep a Comfortable Range of Motion

- Use a complete range that is comfortable for you

Increase the Range of Motion

- Push the exercise until you feel a stretch/ slight discomfort

ROM Exercises and RA

Range-of-motion exercises help maintain normal joint function by increasing and preserving joint mobility and flexibility

They also reduce pain and stiffness. "It's a confidence booster just in terms of being able to be physical, and being able to participate in something that makes you feel good"
- Person on ROM exercises

REMEMBER:

- Move slowly. Try not to bounce
- Breathe
- Count out loud
- Begin exercises slowly doing each exercise a few times only and gradually build up to more
- Try to achieve full range of motion by moving until you feel a slight stretch, but don't force a movement
- STOP exercising if you have severe pain. Deep joint pain and sharp pain in particular should be avoided. Some muscle fatigue or tiredness are expected with an exercise program particularly at first

The ROM exercises shown in this handout stretches all muscles in the body, to better manage your arthritis and improve your health.

HEALTH & FITNESS PROMOTION LAB
Promoting Fitness and Healthy Lifestyles

(514) 398-XXXX | raexercisestudy@gmail.com

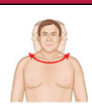
Range of Motion (ROM) Exercises

McGill UNIVERSITY
HEALTH & FITNESS PROMOTION LAB
Promoting Fitness and Healthy Lifestyles

Begin with 5 exercises. As you feel comfortable.

☐ **Neck**

1\.



Turn your head slowly to the right then to the left. Repeat two to four times.

☐ **Neck**

2\.

Tilt your head toward one shoulder then toward the other shoulder. Repeat two to four times.

☐ **Fingers**

3\.

Bend your fingers inward towards your palm then unbend.

☐ **Fingers**

4\.

Next as your fingers bend inward flex your wrist. Keep fingers relaxed. Do not clench fist.

☐ **Fingers**

5\.

Make a tight fist. Then open and relax your hand.

☐ **Finger Spread**

6\.

Open your hand and stretch the fingers as far apart as possible. Bring your fingers together again.

☐ **Finger-to-Thumb**

7\.

One at a time, touch each fingertip to the pad of your thumb.

☐ **Thumb-To-Palm**

8\.

Move your thumb and rest it across your palm. Move it out to the side again.

☐ **Fingers**

9\.

Fold your arm down to rest your hand in your lap. Repeat two times unfolding to shoulder reaching to ceiling returning to lap.

☐ **Palm Up/ Down**

10\.

Tuck your bent elbow against your side. Face your palm down. Turn your palm so that it faces up toward the ceiling. Then turn your palm so it faces down.

☐ **Wrist Bend**

11\.

Bend your hand back toward your wrist so that your fingers point toward the ceiling. Then bend your hand down so that your fingers point down.

☐ **Wrist Rotation**

12\.

Move your hand from side to side. Then roll your hand in circles in one direction. Roll your hand in circles in the other direction.

Begin with 5 exercises. As you feel comfortable.

☐ Arms

13.

Bend your arm at the elbow bringing fingertips towards shoulder. Keep fingers relaxed. Do not clench fist.

☐ Arms

14.

Maintaining this position bring elbow up and then draw imaginary circles in space with your elbow.

☐ Arms

15.

Now unfold your arm at the elbow and reach towards the ceiling.

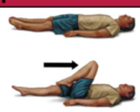
☐ Wrist

16.

Move forward and back at the wrists.

☐ Hip & Knee

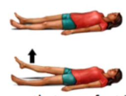
17.



Point your toes. Bend your knee up as close to your chest as possible. Straighten your leg and return it to a flat position on the bed.

☐ Leg Lifts

18.



Raise your leg so that your foot is 6 to 12 inches (15 to 31 centimeters) off the bed. Hold it in the air for a few seconds. Return your leg to the bed.

☐ Legs

19.

Flex your foot so your toes point up toward the ceiling. Move your leg out to the side as far as possible. Bring your leg back to the middle.

☐ Legs

20.

Put your leg flat on the bed. Roll your leg toward the middle so your big toe touches the bed. Then roll your leg out and try to make your smallest toe touch the bed.

☐ Legs

21.

Lie on your back on the bed. Bend your knee so the bottom of your foot is flat on the bed. Slide your heel towards your buttocks. Return your foot to the starting position.

☐ Ankle Bends

22.

Keep your toes on the floor and raise your heel as high as you can. Lower your heel. Then keep your heel on the floor and raise your toes as high as you can.

☐ Ankle Rotation

23.

Raise your foot slightly off the floor. Roll your ankle in circles. Then roll your ankle in circles in the other direction

☐ Gastroc

24.

Stand with right foot back, leg straightm forward leg bent. Keeping heel on floor, turned slightly out, lean into wall until stretch is felt in calf.

Begin with 5 exercises. As you feel comfortable.

☐ Toe Spreads

25.

Spread your toes apart. Bring them together again.

☐ Toe Bend

26.

Curl your toes down toward the sole (bottom) of your foot. Straighten them. Curl them up toward the ceiling. Then straighten them again

☐ Chest & Torso

27. Sit in a chair. With hands on your waist tilt to the right, return to center, then tilt to the left and return to center. Exhale as the movement goes down; inhale as the movement comes up. Don't allow your torso (upper body) to tilt forward. Don't try to hold your head up; instead let it relax to the side.

☐ Abdominals

28.

Pelvic tilt-tighten stomach muscles and flatten the small of your back into the ground.

☐ Abdominals

29.

Do pelvic tilt-hold, lift your head and shoulders, stretch hands towards your knees.

☐ Shoulder

30.

Raise arms forwards and up above your head as far as you can, keeping elbows straight

☐ Shoulder

31.

Move arms out to the side. Try to bring hands together above your head, keeping elbows straight.

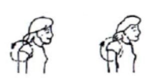
☐ Shoulder

32.

Shrug shoulders up towards your ears then relax.

☐ Shoulder

33.



Circle shoulders up and round backwards, then up and round forwards

☐ Shoulder

34.

Rotation-put hands behind neck, then behind waist, alternately

☐ Shoulder

35.

Appendix D: Tracking Information Sheet

Participant Name: Date:

Week #: Workout #:

Warm-up

Time	5-10 minutes
Intensity	Light-moderate
Type	Elliptical, treadmill, stationary bike

Resistance Exercises

Rest: 1-2 minutes

Exercise	Repetitions	Sets	Set 1 Weight	Set 2 Weight	Set 3 Weight

Cooldown

Time	~ 5 minutes
Type	Foam rolling, stretching

Comments:

Appendix E: Patient characteristic Questionnaire

ID:___________ Visit 1 Date:__________

Date of Birth: (yy/mm/dd) _______ /_______ /______

Sex: ☐ Female ☐ Male

If female, have you reached menopause (no periods for 12 consecutive months) ☐Yes ☐No

Race/ Ethnicity: (✓)

☐ Caucasian ☐ Native North American ☐ Hispanic ☐ Black

☐ Asian ☐ Mixed -specify:________________

☐ Other - specify: ______________________

Employment: (✓)

Which one of the following categories best describes you at the current time?

☐ Working ☐ Unable to work due to illness ☐ Retired

☐ Student ☐ Homemaker ☐ Other:________________

If employed, current occupation (specify):___________________________________

☐ Part-time (≥ 20 hours/week) ☐ Full time (≤20 hours/week)

Highest level of education achieved: (✓)

☐ Some High School ☐ High School ☐ Some College ☐ Completed College

☐ Post Graduate Studies

Smoking: (✓)

Current ☐ Yes (___cig/day) ☐ No

Ex-Smoker ☐ Yes ☐ No Year stopped:_________

In what year were you diagnosed with RA? ______________________

Please list all medicines including supplements that you currently are taking:

Name of medication	Dose	Frequency (times per day)

The following is a list of common health conditions. Please indicate if you currently have the condition the first column. If you do not have the condition, skip to next condition.
If you have the health condition, please indicate in the second column if you receive medications or other types of treatment for it. In the third column indicate if the health condition limits any of your activities. Finally, indicate all medical conditions that are not listed under "other medical problems" at the end of the page.

	Do you have this condition?		Do you receive treatment for it?		Does it limit your activities?	
	No	Yes →	No	Yes →	No	Yes
Heart disease	☐	☐	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐	☐	☐
Lung disease	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐
Ulcers or stomach disease	☐	☐	☐	☐	☐	☐
Kidney disease	☐	☐	☐	☐	☐	☐
Liver disease	☐	☐	☐	☐	☐	☐
Anemia or other blood disease	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐
Depression	☐	☐	☐	☐	☐	☐
Osteoarthritis, degenerative arthritis	☐	☐	☐	☐	☐	☐
Back pain	☐	☐	☐	☐	☐	☐
Fibromyalgia			☐	☐	☐	☐
Other health conditions (please list below)			**No**	**Yes →**	**No**	**Yes**
___________________________________			☐	☐	☐	☐
___________________________________			☐	☐	☐	☐
___________________________________			☐	☐	☐	☐

Appendix F: Multi-dimensional Health Assessment Questionnaire (MDHAQ)

ID:____________ Visit 1 Date:___________

Rapid 3

1. Please check the ONE best answer for your abilities at the time:

Over the last week, were you able to:	**Without ANY difficulty**	**With SOME difficulty**	**With MUCH difficulty**	**Unable to do**
Dress yourself, including tying shoelaces and doing buttons				
Get in and out of bed				
Lift a full cup or glass to your mouth				
Walk outdoors on flat ground				
Wash and dry your entire body				
Bend down to pick up clothing from the floor				
Turn regular faucets on and off				
Get in and out of a car, bus, train, or airplane				
Walk two miles or three kilometers, if you wish				
Participate in recreational activities and sports as you would like, if you wish				

2. How much pain have you had because of your condition OVER the past WEEK?

No Pain | Worst Pain

☐ ☐

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

3. Considering all the ways in which illness and health conditions may affect you at this time. Please indicate below how you are doing:

Very Well | Very Poor

☐ ☐

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

Appendix G: PROMIS-Physical Function 4A

ID:____________ Visit 1 Date:___________

PROMIS29
Please respond to each question or statement by marking one box per row.

Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
Are you able to do chores such as vacuuming or yard work?..........................	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to go up and down stairs at a normal pace?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to go for a walk of at least 15 minutes?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
I felt fearful...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt helpless...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt depressed..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt hopeless..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I have trouble starting things because I am tired..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fatigue

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance

In the past 7 days…	Very poor	Poor	Fair	Good	Very good
My sleep quality was................................	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
My sleep was refreshing...........................	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities

	Never	Rarely	Sometimes	Usually	Always
I have trouble doing all of my regular leisure activities with others..................	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Pain Interference

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How much did pain interfere with your day to day activities?................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix H: Rheumatoid Arthritis Flare Questionnaire (RA-FQ)

ID:____________ Visit 1 Date:___________

RHEUMATOID ARTHRITIS FLARE QUESTIONNAIRE (RA-FQ)

ID:___________________ DATE:_____________

1. Circle the number that best describes the PAIN you felt due to your rheumatoid arthritis <u>during the last week</u>:

No Pain 0—1—2—3—4—5—6—7—8—9—10 Extreme Pain

2. Circle the number that best describes the DIFFICULTY YOU HAD IN DOING PHYSICAL ACTIVITIES (such as using your hands, walking or running, dressing, preparing meals, etc.) due to your rheumatoid arthritis <u>during the last week</u>:

No Difficulty 0—1—2—3—4—5—6—7—8—9—10 Extreme Difficulty

3. Circle the number that best describes how much FATIGUE you felt due to your rheumatoid arthritis <u>during the last week</u>:

No Fatigue 0—1—2—3—4—5—6—7—8—9—10 Extreme Fatigue

4. Circle the number that best describes the STIFFNESS (all over or in your joints) you felt due to your rheumatoid arthritis <u>during the last week</u>:

No Stiffness 0—1—2—3—4—5—6—7—8—9—10 Extreme Stiffness

5. Considering how active your rheumatoid arthritis has been, please circle the number that best describes the difficulty you had when TAKING PART IN ACTIVITIES SUCH AS WORK, FAMILY LIFE, SOCIAL EVENTS that are typical for you <u>during the last week</u>:

No Difficulty 0—1—2—3—4—5—6—7—8—9—10 Extreme Difficulty

6. Have you had this level of the above symptoms for more than one week? Yes ☐ No ☐

7. Are you having a flare (flare-up) of rheumatoid arthritis at this time? Yes ☐ No ☐

Appendix I: Exercise Self-Efficacy Scale (ESES) and Physical Activity Enjoyment Scale (PACES)

ID:____________ Visit 1 Date:___________

Please select a number that describes how confident you are that you can exercise…

1.…In spite of your work schedule

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

2.---when physically fatigued

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

2.…when exercise is boring

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

4.….with minor injuries

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

5…In spite of other time demands

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

6…In spite of family responsibilities

Not Certain 0 1 2 3 4 5 6 7 8 9 10 Very Certain

Please rate how you feel at the moment about physical activity

1	Unpleasurable	1	2	3	4	5	6	7	Pleasurable
2	No fun at all	1	2	3	4	5	6	7	A lot of fun
3	Not at all pleasant	1	2	3	4	5	6	7	Pleasant
4	Not at all invigorating	1	2	3	4	5	6	7	Invigorating
5	Not at all gratifying	1	2	3	4	5	6	7	Gratifying
6	Not at all exhilarating	1	2	3	4	5	6	7	Exhilarating
7	Not at all stimulating	1	2	3	4	5	6	7	Very stimulating
8	Not at all refreshing	1	2	3	4	5	6	7	Very refreshing

Appendix J: International Physical Activity Questionnaire – Short Form (IPAQ - SF)

ID:____________ Visit 1 Date:___________

International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____days per week

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____hours per day

   _____minutes per day

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____days per week

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____hours per day

_____minutes per day

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____days per week

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____hours per day

_____minutes per day

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____hours per day

_____minutes per day

☐ Don't know/Not sure