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Review

Myokine Response to Resistance Exercise in Older Adults and the Similarities and Differences to Younger Adults: A Brief Narrative Review

Dean M. Cordingley [1, 2], Stephen M. Cornish [1, 3, 4, *]

1. Applied Health Sciences Program, University of Manitoba, Winnipeg, Manitoba, R3T 2N2, Canada; E-Mails: umcordid@myumanitoba.ca; Stephen.Cornish@umanitoba.ca
2. Pan Am Clinic Foundation, 75 Poseidon Bay, Winnipeg, Manitoba, R3M 3E4, Canada
3. Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, Manitoba, R3T 2N2, Canada
4. Centre on Aging, University of Manitoba, Winnipeg, Manitoba, R2T 2N2, Canada

* **Correspondence:** Stephen M. Cornish; E-Mail: Stephen.Cornish@umanitoba.ca

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Abstract

Myokines are cytokines secreted from muscle during contraction and are implicated in autocrine, paracrine, and endocrine regulation of biological systems. It is postulated that myokines contribute to skeletal muscle adaptations in response to resistance exercise. Exercise, including resistance exercise, is an important factor in the management of maintaining skeletal muscle strength, mass, and function with aging. Sarcopenia is exacerbated with increased age and therefore, it is important to understand the potential underlying mechanisms whereby exercise may be beneficial in reducing the consequences of sarcopenia for older adults. Myokine secretion is one mechanism which is postulated to account for the benefits of exercise in aging muscle. The response of myokines to aerobic exercise in older adults have previously been reviewed; however, there is limited research focused on the response of myokines to resistance exercise. Therefore, the aim of this narrative review is to discuss the response of various myokines to an acute bout of resistance

exercise and/or chronic resistance exercise training in older adults, compare the response between younger and older adults, and briefly outline the influence myokines may have on skeletal muscle adaptations.

Keywords
Cytokine; resistance training; muscle hypertrophy; older adult

1. Introduction

Sarcopenia refers to the age related loss of muscle mass, strength and performance which are associated with respiratory disease [1], heart failure [2], quality of life, health care costs [3], activities of daily living [4], and falls and fractures [5]. Exercise, and in particular resistance exercise, is one component suggested for the prevention and treatment of sarcopenia [6]. It has been postulated that myokines may be responsible for improvements in skeletal muscle health in response to exercise in older adults either in an autocrine or paracrine fashion [7].

Myokines are proteins and polypeptides, of which some are part of the cytokine family, and are secreted from skeletal muscle [8]. Myokines are sometimes referred to as “exerkines” because of their secretion with exercise and are considered as potential modulators of exercise mediated health improvements; however, exerkines can be released from multiple types of tissue [9, 10]. Certain myokines are correlated with changes in muscle strength, mass and strength per kg of fat free mass in response to resistance exercise [11]. An individual’s myokine response to exercise may contribute to the benefits of exercise in managing sarcopenia [7]. However, most research to date has investigated the myokine response in older adults to aerobic type exercise (i.e., walking, running, cycling) with fewer studies investigating the response to resistance exercise [7]. Resistance exercise is a potent stimulus for myokine secretion in younger adults [12]; therefore, the purpose of this review is to outline the response of select myokines to resistance exercise in older adults and compare this response to younger adults.

2. Discussion

2.1 Interleukin-6 (IL-6)

Interleukin-6 (IL-6) was one of the first molecules to be proposed as a myokine as it is secreted from skeletal muscle and can exert effects on other biological organs [10]. IL-6 is primarily known for its pro-inflammatory characteristics, however when secreted in response to skeletal muscle contraction it results in anti-inflammatory effects by signaling the release of other anti-inflammatory type cytokines such as IL-1 receptor antagonist and IL-10 [13]. Additionally, aside from being anti-inflammatory, which is likely beneficial for preserving muscle mass in older age, IL-6 is postulated to contribute to muscle hypertrophy in response to resistance exercise training (for review see [14]). In humans, the acute response of IL-6 to a bout of resistance training has been found to significantly correlate with muscle hypertrophy in response to a resistance training program in young and older men [11, 15]. Mechanistically, from an animal model, IL-6 may encourage hypertrophy by stimulating skeletal muscle satellite cell proliferation and myogenic

differentiation [16]. Following muscle damage from eccentric skeletal muscle actions in humans, signal transducer and activator of transcription 3 protein (STAT3), within the nuclei of skeletal muscle satellite cells, is induced by IL-6 suggesting satellite cell proliferation [17]. In a cultured myotube model, IL-6 can also signal the stimulation of mammalian target of rapamycin complex 1 (mTORC1), which is one of the main mechanisms driving protein synthesis in skeletal muscle [18]. Although the data is limited, the response of IL-6 to a bout of resistance exercise is similar between younger and older males regardless of the training status (i.e., untrained or trained) of the individual [11, 19].

Particularly important with aging is the ability of resistance training to be anti-inflammatory which could help slow muscle atrophy. With progressing age a human experiences numerous stressors, which in combination with genetics and the environment often results in an increased pro-inflammatory state known as "inflammaging" [20]. In a group of 986 older men and women (mean age ± SD: 74.6 ± 6.2 yrs) it was found that higher levels of IL-6 were associated with a 2 to 3-fold greater risk of muscle strength losses over a 3-year period [21]. A study investigating an 8-week resistance training program in obese (41.0 ± 6.2% body fat) older women (age, 68.2 ± 4.2 yrs) found that a whole body resistance training program performed 3-days per week resulted in decreased resting IL-6 compared to the control group [22]. Interestingly, high amounts of adipose tissue, as found in overweight/obesity, are associated with a pro-inflammatory state which includes high concentrations of circulating IL-6; however, aerobic exercise training, at least in a murine model, is able to promote increased lipolysis in visceral adipose tissue via activation of the lipolytic pathway by skeletal muscle derived IL-6 [23]. Although adipose tissue can produce high levels of IL-6, it has been suggested it is the secretion of tumour necrosis factor-alpha (TNF-α) which can stimulate the release of IL-6 from adipose tissue. In this case, TNF-α is the pro-inflammatory cytokine which induces metabolic disease and likely drives the increase in IL-6 [24]. Also, it may be different isoforms of IL-6 are released from muscle, adipose tissue, or inflammatory cells and these isoforms have various roles to play physiologically or pathophysiologically [24]. It is proposed that physical activity can play an important role in promoting longevity [20], with current evidence suggesting the response of IL-6 to acute and chronic exercise being one possible mechanism of action to reduce chronic inflammation via stimulation of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist.

2.2 Myostatin

Myostatin is a member of the transforming growth factor beta (TGF-β) super family and down regulates muscle growth [25]. In a murine model, inhibition of myostatin gene expression results in individual muscles with a 2-3 times greater mass than in wild-type animals [25]. Insulin-like growth factor 1 (IGF-1) activity is antagonized by myostatin on the protein kinase B (Akt) pathway [26]. Myostatin signaling inhibits the activation of the Akt/mammalian target of rapamyacin (mTOR)/p70S6k pathway resulting in decreased myoblast differentiation and myotube hypertrophy [27], and decreased protein synthesis [28]. In a murine model of resistance exercise, myostatin signaling was decreased by the activation of the TGF-β inhibitor termed Notch which resulted in a decrease in transcriptional activity of myostatin and increased hypertrophy [29]. Thus, resistance exercise results in myostatin inhibition [30].

One study has compared myostatin messenger ribonucleic acid (mRNA) expression from muscle biopsies in younger (n = 8; age, 23 ± 2 yrs) and older (n = 6; age, 85 ± 1 yrs) women prior to and following completion of bilateral knee extensions for 3 sets of 10 repetitions at 70% of their one repetition maximum strength (1-RM) [31]. It was observed that at rest older women had a higher expression of myostatin compared to the younger, however the bout of resistance exercise had a similar effect on myostatin gene expression (2.2-fold down regulation at 4 hours post-exercise) for both age groups. Another study which compared sarcopenic and nonsarcopenic older and not older males (n = 31; age range: 55-70 yrs) found that 8-weeks of progressive resistance exercise training resulted in decreased myostatin at rest for both the sarcopenic and nonsarcopenic individuals [32]. However, in contrast, a study investigating the effects of elastic band resistance training on circulating markers of muscle growth and degradation in older women (n = 91; mean age = 83.6 yrs, age range = 65-92 yrs) found that myostatin remained unchanged following 3 and 6-months of training [33]. These two results combined suggest that myostatin levels may respond differently between older males and females completing resistance-exercise training; however, further research would be needed to confirm this. This could be explained by altered hormonal concentrations (such as testosterone and estrogen) between males and females and may also be explained by the vastly different age categories these two studies were completed in (i.e., males age range 55-70 years and females age range 65-92 years) [32, 33].

2.3 Follistatin

Follistatin is a myostatin antagonist and also inhibits activin (another promoter of muscle catabolism) within skeletal muscle [34]. Follistatin results in muscle hypertrophy from the inhibition of myostatin and activin and by promoting satellite cell proliferation [34]. The up-regulation of follistatin is associated with satellite cell proliferation stimulated via testosterone [35]. Additionally, follistatin increases myogenic differentiation [36]. Therefore, follistatin may be an important myokine in skeletal muscle hypertrophy, while improving muscle healing from injury and disease [36].

The response of follistatin to resistance training programs may differ between sarcopenic and nonsarcopenic individuals. Following an 8-week progressive resistance training program in a mix of middle-age and older males (n = 31; age, 55-70 yrs), only the healthy, nonsarcopenic individuals, showed an elevated follistatin concentration post-training [32]. Thus, if an individual already has low skeletal muscle mass, they may not respond as readily to resistance-exercise in terms of enhancing follistatin concentrations. This may be due to anabolic resistance (i.e., the lack of response to anabolic stimuli) that older sarcopenic males may possess [37]. This may be further explained by the decrease in IGF-1 and decreased activation of the Akt/mTOR pathway in aging muscle [37]. Another study investigated follistatin concentrations following 3 and 6-months of elastic band resistance training in older women (n = 91; mean age = 83.6 yrs, range = 65-92 yrs) [33]. It was determined that the resistance training program resulted in increased circulating follistatin, but only at the 6-month mark of the training program. This proposes that it may take a longer period to see increased concentrations of follistatin from the resistance training stimulus in older women.

2.4 Irisin

The myokine irisin is primarily recognized for its effect on converting white adipose tissue to brown adipose tissue (which is more metabolically active) [38]. However, emerging evidence suggests irisin may also contribute to muscle hypertrophy [39]. While undergoing myogenic differentiation, cultured human myocytes increase fibronectin type III domain-containing protein 5 (FNDC5) expression and irisin secretion [39]. Additionally, when human myocytes are treated with irisin an increase in IGF-1 gene expression and a decrease in myostatin gene expression occurs [39]. These findings suggest that irisin may contribute to muscle hypertrophy in response to resistance exercise.

The response of irisin to acute resistance exercise as well as resistance training programs in older adults has been investigated [11, 40]. In both resistance untrained and trained states (i.e., before and after a 12-week resistance training program), younger males (n = 8; age: 24.8 ± 3.9 yrs) have greater concentrations of circulating irisin than older males (n = 7; age: 68.3 ± 5.0 yrs) [11]. However, in the untrained state younger and older adults do not differ in their response to a bout of blood flow restricted resistance exercise but following a 12-week resistance training program differences appear where younger males have higher concentrations of circulating irisin immediately following, 24-hrs and 48-hrs following the blood flow restricted resistance exercise [11]. Another study, also conducted in older males, randomized participants to a control group (n = 7; age: 61.9 ± 3.1 yrs) or a group which completed 12-weeks of resistance training (n = 10; age: 62.3 ± 3.5 yrs) and found that the resistance training program resulted in elevated resting serum irisin concentrations, as well as the irisin concentrations in the resistance training group were negatively correlated with the change in percent body fat over the 12-week program [40]. This suggests that irisin may have a positive effect on reducing fat mass in older males completing a resistance training program.

2.5 Brain Derived Neurotropic Factor (BDNF)

Brain derived neurotrophic factor (BDNF) was initially recognized for its relationship with nervous system function, however BDNF and its receptors are expressed in skeletal muscle [41]. This would suggest that BDNF could play an important role in skeletal muscle [42]. In murine skeletal muscle, BDNF is present in satellite cells and is important for satellite cell differentiation and skeletal muscle regeneration [43]. Injured murine muscle tissue depleted of BDNF has delayed expression of regeneration related molecules and formation of new muscle fibers [43]. Exercise (cycling for 120 mins at 60% of maximal oxygen uptake) results in upregulation of BDNF expression in human skeletal muscle [44] and therefore may contribute to skeletal muscle and neuronal adaptations to aerobic training in older adults.

A group of cognitively healthy older adults (males, n = 5 and females, n = 5; age: 66.3 ± 5.3 yrs) had blood samples collected at rest and acutely following a resistance training protocol which was performed at study initiation and again following 8-weeks of resistance training [45]. The authors identified an acute increase of circulating BDNF following resistance exercise, however there was no difference in systemic concentrations at rest or following the 8-week resistance training program. Another 12-week resistance training study randomized apparently healthy older adults (n = 56; age: 68 ± 5 yrs) to 3 days per week at either a high (2 sets of 10-15 repetitions performed at 80% of their 1-RM), low (1 set of 80-100 repetitions at 20% of their 1-RM) or mixed low-resistance (1 set of 60 repetitions at 20% 1-RM followed by 1 set of 10-20 repetitions at 40% 1-RM) and were

instructed to reach volitional exhaustion in each set they completed [46]. The study found that only the males in the group which performed the mixed low-resistance program increased resting serum BDNF, while no other changes were identified. These results suggest that BDNF secretion may be sex and resistance intensity dependent. However, contrasting these previous findings, evidence suggests that BDNF can acutely increase following resistance training, as well as be higher at rest following a resistance training program in women [47, 48]. One study evaluated serum BDNF concentrations in older females (n = 20; age: 84 ± 8 yrs) from a nursing home who were randomly assigned to elastic resistance training or a control group [48]. It was found that both at rest and following an acute bout of elastic resistance training BDNF was increased. Another study investigated the effects of a 12-week resistance training program (performed 3-days per week with elastic bands) in a group of 26 older females (age: 70.6 ± 6.2 yrs) with obesity (body fat percentage: 36.1 ± 2.5%) [47]. The group which performed the resistance training had higher serum BDNF concentrations at rest, following the training program, compared to the females who did not. These results suggest that resistance exercise is beneficial for increasing BDNF concentrations in females which may have many positive effects on many physiological systems (for example: muscle and nerve tissue). In nervous tissue, BDNF is deemed one of the candidate molecules that may have an effect in enhancing neurogenesis and synaptic plasticity [49]; however, skeletal muscle derived BDNF may not be able to cross the blood-brain-barrier thus, may have limited effects in the central nervous system but, BDNF levels seem to be enhanced in human models of acute exercise in the central nervous system [50]. In skeletal muscle tissue, BDNF may act in an autocrine role by enhancing lipid oxidation via adenosine monophosphate activated protein kinase (AMPK) which would increase the breakdown of intramuscular lipid stores [50].

3. Conclusions

Myokines are postulated to contribute to the hypertrophic effects of skeletal muscle associated with exercise [14] with many myokines preferentially up- or down-regulated in response to resistance exercise [12]. Exercise induced myokine expression may be specifically valuable in older age because of the variety of therapeutic roles they may play in maintaining health with increasing age [7]. This review highlighted the effects of resistance exercise on various myokines in older adults, and specifically their potential influence on skeletal muscle (see Table 1 for summary of discussed human studies). Sarcopenia is a concern in older age and is associated with additional health risks [1-5]. Resistance exercise is recognized as a potent stimulus for muscle hypertrophy, strength and protein synthesis which could mitigate strength loss, muscle atrophy and loss of function with aging [6]. The current literature investigating the myokine response to acute and chronic resistance exercise in older adults is limited, but a further understanding of these proteins could be beneficial for identifying mechanisms for therapeutic targets. The current literature utilizes resistance training protocols of various frequencies, intensities, types (i.e., free weights, machines, elastic bands), and durations which may explain some of the contradicting findings. Identifying the optimal resistance training sessions and programs to stimulate hypertrophy related myokine secretion would improve recommendations for aging adults at risk of or experiencing the loss of muscle strength, muscle mass and function. It is suggested that further research around myokine biology in relation to resistance exercise will enhance our understanding of how myokines may influence skeletal muscle in a positive manner.

Table 1 Response of myokines to resistance exercise in human older adults.

Author	Design	Sample	Intervention	Main Results	Conclusions
Interleukin-6 (IL-6)					
Cordingley et al. (2022) [11]	Pre-post, non-randomized, uncontrolled study	Younger males, n = 8, age = 24.8 ± 3.9 yrs; Older males, n = 7, age = 68.3 ± 5.0 yrs	A bout of BFR-RE (upper and lower body) was performed before and after a 12-week RT program. Blood samples were collected prior to, immediately after and at 3, 6, 24 and 48-hours following the bout of BFR-RE.	Circulating IL-6 peaked above baseline immediately following BFR-RE ($p = 0.005$) but no differences were observed between older and younger males in the untrained or trained state.	Systemic IL-6 concentrations do not differ between younger and older males following a bout of BFR-RE.
Della Gatta et al. (2014) [19]	Pre-post, non-randomized, uncontrolled study	Younger males, n = 8, age - 20.3 ± 0.8 yrs; Older males, n = 8, 66.9 ± 1.6 yrs	Isokinetic knee extension/flexion exercise was performed before and following the completion of a 12-weeks of full body RT. Muscle biopsies were collected at rest and 2-hours after the isokinetic knee extension/flexion exercise.	Resting IL-6 expression was not different between groups before or following the RT program. IL-6 expression was higher 2-hours following exercise compared to rest, but was not different between older and younger males in the trained or untrained state.	IL-6 expression was not different at rest or following resistance exercise in younger or older males before or after a 12-week RT program.
Schaap et al. (2006) [21]	Prospective cohort study	Older males and females, n = 986, age =	Serum IL-6 was measured at baseline. Muscle strength (grip strength) and muscle mass (DEXA)	Higher circulating IL-6 is associated with greater decreases in muscle strength. High concentrations of IL-6 (>5 pg/mL) is associated with a 2 to	Higher levels of IL-6 are associated with greater loss of muscle strength in older males and females.

		74.6 ± 6.2 yrs	were assessed at baseline and 3-years later.	3-fold increased risk of losing >40% muscle strength. No associations between IL-6 and change in muscle mass was identified.	
Tomeleri et al. (2016) [22]	RCT	Obese older females, n = 38, age = 68.2 ± 4.2 yrs	Resting blood samples were collected before and after an 8-week full-body RT program.	The 8-week RT program resulted in decreased resting IL-6 concentrations (baseline = 4.0 ± 1.9 pg/mL vs. post-RT = 3.3 ± 1.2 pg/mL) while there was no change in the control group.	Eight-weeks of RT is effective in decreasing resting IL-6 concentration in older obese females.
Myostatin					
Raue et al. (2006) [31]	Pre-post, non-randomized, uncontrolled study	Younger females, n = 8; age, 23 ± 2 yrs; Older females, n = 6; age, 85 ± 1 yrs	Muscle biopsies were collected before and 4-hours after completing knee extension exercise (3 sets of 10 repetitions at 70% of one-repetition maximal strength).	At rest (prior to resistance exercise) older females had 56% greater myostatin gene expression compared to younger females. Following resistance exercise, myostatin expression was down regulated 2.2-fold with no difference between younger and older females.	Older females have higher resting expression of myostatin in skeletal muscle compared to younger females, but the response to a bout of resistance exercise is similar in both older and younger females.
Negaresh et al. (2019) [32]	Pre-post, non-randomized, uncontrolled study	Older and not-older males with and without sarcopenia, n = 31; age range: 55-70 yrs	Blood samples were collected prior to and 3-days following the completion of an 8-week RT protocol which incorporated upper and lower body exercises.	Eight-weeks of RT resulted in decreased myostatin in both sarcopenic and non-sarcopenic males. There was no difference between groups either before or after RT.	Older and non-older males with and without sarcopenia have similar concentrations of systemic myostatin. Completing an 8-week RT program was sufficient to decrease circulating myostatin at rest.

Hofmann et al. (2016) [33]	RCT	Older females, n = 91; mean age = 83.6 yrs, age range = 65-92 yrs	Participants completed either RT (elastic band training for all major muscle groups), RT and received a nutritional supplement each morning and following RT (contained 20.7 g protein, 9.3 g carbohydrates, 3 g fat, 800 IU vitamin D, 2.9 mg vitamin B6, 3 µg vitamin B12, and minerals) or cognitive training (control group) for 6-months. Resting blood samples were collected at baseline, 3 and 6-months.	Myostatin remained unchanged in all groups at all time-points.	Six-months of elastic band based resistance exercise does not change resting concentrations of systemic myostatin in older females.
Follistatin					
Negaresh et al. (2019) [32]	Pre-post, non-randomized, uncontrolled study	Older and not-older males with and without sarcopenia, n = 31; age range: 55-70 yrs	Blood samples were collected prior to and 3-days following the completion of an 8-week RT protocol which incorporated upper and lower body exercises.	Eight-weeks of RT resulted in increased follistatin in both sarcopenic and non-sarcopenic males. There was no difference between groups either before or after RT.	Older and non-older males with and without sarcopenia have similar concentrations of systemic follistatin. Completing an 8-week RT program was sufficient to increase circulating follistatin at rest.

Hofmann et al. (2016) [33]	RCT	Older females, n = 91; mean age = 83.6 yrs, age range = 65-92 yrs	Participants completed either RT (elastic band training for all major muscle groups), RT and received a nutritional supplement each morning and following RT (contained 20.7 g protein, 9.3 g carbohydrates, 3 g fat, 800 IU vitamin D, 2.9 mg vitamin B6, 3 µg vitamin B12, and minerals) or cognitive training (control group) for 6-months. Resting blood samples were collected at baseline, 3 and 6-months.	Resting follistatin increases with 6-months of elastic band RT (median (range); baseline = 1.92 (1.38-2.86) ng/mL, 3-months = 2.00 (1.29-3.09) ng/mL, and 6-months = 2.23 (1.34-3.61) ng/mL; p = 0.008), however RT combined with a multi-ingredient nutritional supplement (p = 0.882), and cognitive training (p = 0.084) do not.	Elastic band RT alone for 6-months increases resting circulating follistatin, but RT combined with a multi-ingredient nutritional supplement does not.
Irisin					
Cordingley et al. (2022) [11]	Pre-post, non-randomized, uncontrolled study	Younger males, n = 8, age = 24.8 ± 3.9 yrs; Older males, n = 7, age = 68.3 ± 5.0 yrs	A bout of BFR-RE was performed (upper and lower body) before and after a 12-week RT program. Blood samples were collected prior to, immediately after and at 3, 6, 24 and 48-hours following the bout of BFR-RE.	No differences in circulating irisin following BFR-RE in the untrained state between the younger and older males. Following 12-weeks of RT, younger males have higher concentrations of irisin up to 48-hours following BFR-RE.	In the untrained state, younger and older males have a similar response in irisin to a bout of BFR-RE. However, in the trained state, younger males have a more robust response compared to older males.

Zhao et al. (2017) [40]	RCT	Older males; n = 17; Control group, age = 61.9 ± 3.1 yrs; RT group, age = 62.3 ± 3.5	Blood samples were collected before and after a 12-week RT program (or control period) which consisted of lower body and core muscle training.	RT resulted in an increased concentration of resting serum irisin (before = 287.0 ± 143.5 ng/mL vs. after = 556.0 ± 126.6 ng/mL; $p < 0.01$) but there was no change in the control group (before = 337.1 ± 137.8 ng/mL vs. after = 327.1 ± 146.9 ng/mL). Additionally, change in resting irisin from was correlated with change in body fat percentage following the 12-week RT program ($r = -0.705$, $p < 0.05$).	A 12-week lower body and core muscle RT program increases resting irisin concentrations in older males.
Brain derived neurotropic factor (BDNF)					
Walsh et al. (2016) [45]	Pre-post, non-randomized, uncontrolled study	Older adults; males, n = 5; females, n = 5; age: 66.3 ± 5.3 yrs	Blood samples were collected at rest, immediately following as well as 10, 20, 30, 40, 60, and 120 minutes after a bout of resistance exercise. This protocol was completed prior to and after an 8-week lower body RT program.	BDNF increased immediately following the bout of resistance exercise both before and after the RT program. There was no difference in BDNF concentrations at any time point when the untrained and trained conditions were compared.	An 8-week lower body RT program does not change resting or the resistance exercise induced response of BDNF in older males and females.
Forti et al. (2015) [46]	Randomized, non-controlled, study	Older adults; male, n = 24; female,	Blood samples were collected before and following 12-weeks of RT (lower and upper body) at either a high load (2 sets	Only older males who completed the mixed low-load RT experienced changes in resting circulating BDNF (before = 34.9 ± 10.7 ng/mL vs. after = 42.9 ± 11.9 ng/mL; $p = 0.013$).	Only a mixed low-load RT program resulted in increased systemic BDNF concentrations in male participants.

		n = 25; age: 68 ± 5 yrs	of 10-15 repetitions performed at 80% of their 1-RM), low load (1 set of 80-100 repetitions at 20% of their 1-RM) or mixed low load (1 set of 60 repetitions at 20% 1-RM followed by 1 set of 10-20 repetitions at 40% 1-RM).	Males and females who completed the high and low load RT, along with females who completed the mixed low-load RT did not experience changes in circulating BDNF.	
Roh et al. (2020) [47]	RCT	Older females with obesity; n = 26; 70.6 ± 6.2 yrs	Participants were randomized to complete upper and lower body elastic band RT (intensity of 10-14 out of 20 based on rating of perceived exertion scale) for 12-weeks or were randomized to the control group. Blood samples were collected prior to and following the 12-week RT program.	The group which completed the RT had higher resting BDNF concentrations after the 12-week intervention than the control group (RT group, before = 1.55 ± 0.26 ng/mL vs. after = 1.61 ± 0.22ng/mL; Control, before = 1.43 ± 0.16 ng/mL vs. after = 1.32 ± 0.18ng/mL; $p < 0.001$).	Twelve-weeks or elastic band based RT results in greater BDNF at rest compared to a control group in older females with obesity.
Urzi et al. (2019) [48]	RCT	Older female nursing home residents; n	Participants were randomized to RT (moderate intensity (based on rating of perceived exertion) elastic band RT) or control group	No changes in BDNF were observed at any time point for the control group. In response to a single resistance exercise bout, BDNF increases immediately after exercise completion and returns to baseline	Acutely, elastic band resistance exercise stimulates increased circulating BDNF immediately following exercise, while 12-weeks

	= 20; age: 84 ± 8 yrs	for 12-weeks. Blood samples were collected before and after completion of the RT program. As well, samples were collected at the 4th resistance exercise session at rest, immediately following, and 2-hours after.	by 2-hours (rest = 1.89 ± 0.86 ng/mL vs. post = 2.42 ± 0.92 ng/mL vs. 2-hours post = 1.96 ± 1.20 ng/mL; p = 0.04). The 12- week RT program resulted in an increased circulating BDNF (Before = 1.89 ± 0.86 ng/mL vs. after = 2.32 ± 0.86 ng/mL; p = 0.02) compared to the control group.	of elastic band RT results in increased resting BDNF concentrations for older females nursing home residents.

BFR-RE, blood flow restricted resistance exercise; DEXA, dual-energy x-ray absorptiometry; RCT, randomized controlled trial; RT, resistance training; 1-RM, one repetition maximum strength

Author Contributions

SMC conceptualized the manuscript. SMC and DMC contributed to writing of the original manuscript and have reviewed and agreed to the published version of the manuscript.

Competing Interests

DMC is affiliated with the Pan Am Clinic Foundation which receives general education and research support from ConMed Linvatec, Ossur, Zimmer Biomet, and Arthrex. SMC declares no competing interests exist.

References

1. Bone AE, Hepgul N, Kon S, Maddocks M. Sarcopenia and frailty in chronic respiratory disease: Lessons from gerontology. Chron Respir Dis. 2017; 14: 85-99.
2. Curcio F, Testa G, Liguori I, Papillo M, Flocco V, Panicara V, et al. Sarcopenia and heart failure. Nutrients. 2020; 12: 211.
3. Mijnarends DM, Luiking YC, Halfens RJ, Evers SM, Lenaerts EL, Verlaan S, et al. Muscle, health and costs: A glance at their relationship. J Nutr Health Aging. 2018; 22: 766-773.
4. Wang DX, Yao J, Zirek Y, Reijnierse EM, Maier AB. Muscle mass, strength, and physical performance predicting activities of daily living: A meta-analysis. J Cachexia Sarcopenia Muscle. 2020; 11: 3-25.
5. Yeung SS, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CG, et al. Sarcopenia and its association with falls and fractures in older adults: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2019; 10: 485-500.
6. Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med. 2019; 132: 42-49.
7. Kwon JH, Moon KM, Min KW. Exercise-induced myokines can explain the importance of physical activity in the elderly: An overview. Healthcare. 2020; 8: 378.
8. Pedersen BK, Åkerström TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. J Appl Physiol. 2007; 103: 1093-1098.
9. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, et al. Exerkines in health, resilience and disease. Nat Rev Endocrinol. 2022; 18: 273-289.
10. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al. Searching for the exercise factor: Is IL-6 a candidate? J Muscle Res Cell Motil. 2003; 24: 113-119.
11. Cordingley DM, Anderson JE, Cornish SM. Myokine response to blood-flow restricted resistance exercise in younger and older males in an untrained and resistance-trained state: A pilot study. J Sci Sport Exerc. 2022. doi:10.1007/s42978-022-00164-2.
12. Zunner BE, Wachsmuth NB, Eckstein ML, Scherl L, Schierbauer JR, Haupt S, et al. Myokines and resistance training: A narrative review. Int J Mol Sci. 2022; 23: 3501.
13. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. Physiol Rev. 2008; 88: 1379-1406.
14. Cornish SM, Bugera EM, Duhamel TA, Peeler JD, Anderson JE. A focused review of myokines as a potential contributor to muscle hypertrophy from resistance-based exercise. Eur J Appl Physiol. 2020; 120: 941-959.

15. Mitchell CJ, Churchward-Venne TA, Bellamy L, Parise G, Baker SK, Phillips SM. Muscular and systemic correlates of resistance training-induced muscle hypertrophy. PloS One. 2013; 8: e78636.
16. Begue G, Douillard A, Galbes O, Rossano B, Vernus B, Candau R, et al. Early activation of rat skeletal muscle IL-6/STAT1/STAT3 dependent gene expression in resistance exercise linked to hypertrophy. PloS One. 2013; 8: e57141.
17. Toth KG, McKay BR, De Lisio M, Little JP, Tarnopolsky MA, Parise G. IL-6 induced STAT3 signalling is associated with the proliferation of human muscle satellite cells following acute muscle damage. PLoS One. 2011; 6: e17392.
18. Gao S, Durstine JL, Koh HJ, Carver WE, Frizzell N, Carson JA. Acute myotube protein synthesis regulation by IL-6-related cytokines. Am J Physiol Cell Physiol. 2017; 313: C487-C500.
19. Della Gatta PA, Garnham AP, Peake JM, Cameron-Smith D. Effect of exercise training on skeletal muscle cytokine expression in the elderly. Brain Behav Immun. 2014; 39: 80-86.
20. Fulop T, Larbi A, Pawelec G, Khalil A, Cohen AA, Hirokawa K, et al. Immunology of aging: The birth of inflammaging. Clin Rev Allergy Immunol. 2021. doi:10.1007/s12016-021-08899-6.
21. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006; 119: 526.e9-526.e17.
22. Tomeleri CM, Ribeiro AS, Souza MF, Schiavoni D, Schoenfeld BJ, Venturini D, et al. Resistance training improves inflammatory level, lipid and glycemic profiles in obese older women: A randomized controlled trial. Exp Gerontol. 2016; 84: 80-87.
23. Bertholdt L, Gudiksen A, Ringholm S, Pilegaard H. Impact of skeletal muscle IL-6 on subcutaneous and visceral adipose tissue metabolism immediately after high-and moderate-intensity exercises. Pflugers Arch. 2020; 472: 217-233.
24. Pedersen BK, Steensberg A, Schjerling P. Muscle-derived interleukin-6: Possible biological effects. J Physiol. 2001; 536: 329-337.
25. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-p superfamily member. Nature. 1997; 387: 83-90.
26. Morissette MR, Cook SA, Buranasombati C, Rosenberg MA, Rosenzweig A. Myostatin inhibits IGF-I-induced myotube hypertrophy through Akt. Am J Physiol Cell Physiol. 2009; 297: 1124-1132.
27. Trendelenburg AU, Meyer A, Rohner D, Boyle J, Hatakeyama S, Glass DJ. Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. Am J Physiol Cell Physiol. 2009; 296: C1258-C1270.
28. Taylor WE, Bhasin S, Artaza J, Byhower F, Azam M, Willard Jr DH, et al. Myostatin inhibits cell proliferation and protein synthesis in C_2C_{12} muscle cells. Am J Physiol Endocrinol Metab. 2001; 280: E221-E228.
29. MacKenzie MG, Hamilton DL, Pepin M, Patton A, Baar K. Inhibition of myostatin signaling through Notch activation following acute resistance exercise. PloS One. 2013; 8: e68743.
30. Allen DL, Hittel DS, McPherron AC. Expression and function of myostatin in obesity, diabetes, and exercise adaptation. Med Sci Sports Exerc. 2011; 43: 1828-1835.
31. Raue U, Slivka D, Jemiolo B, Hollon C, Trappe S. Myogenic gene expression at rest and after a bout of resistance exercise in young (18-30 yr) and old (80-89 yr) women. J Appl Physiol. 2006; 101: 53-59.

32. Negaresh R, Ranjbar R, Baker JS, Habibi A, Mokhtarzade M, Gharibvand MM, et al. Skeletal muscle hypertrophy, insulin-like growth factor 1, myostatin and follistatin in healthy and sarcopenic elderly men: The effect of whole-body resistance training. Int J Prev Med. 2019; 10: 10-29.
33. Hofmann M, Schober-Halper B, Oesen S, Franzke B, Tschan H, Bachl N, et al. Effects of elastic band resistance training and nutritional supplementation on muscle quality and circulating muscle growth and degradation factors of institutionalized elderly women: The Vienna Active Ageing Study (VAAS). Eur J Appl Physiol. 2016; 116: 885-897.
34. Gilson H, Schakman O, Kalista S, Lause P, Tsuchida K, Thissen JP. Follistatin induces muscle hypertrophy through satellite cell proliferation and inhibition of both myostatin and activin. Am J Physiol Endocrinol Metab. 2009; 297: E157-E164.
35. Braga M, Bhasin S, Jasuja R, Pervin S, Singh R. Testosterone inhibits transforming growth factor-β signaling during myogenic differentiation and proliferation of mouse satellite cells: Potential role of follistatin in mediating testosterone action. Mol Cell Endocrinol. 2012; 350: 39-52.
36. Zhu J, Li Y, Lu A, Gharaibeh B, Ma J, Kobayashi T, et al. Follistatin improves skeletal muscle healing after injury and disease through an interaction with muscle regeneration, angiogenesis, and fibrosis. Am J Pathol. 2011; 179: 915-930.
37. Endo Y, Nourmahnad A, Sinha I. Optimizing skeletal muscle anabolic response to resistance training in aging. Front Physiol. 2020; 11: 874.
38. Shan T, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1α-Fndc5 pathway in muscle. FASEB J. 2013; 27: 1981-1989.
39. Huh JY, Dincer F, Mesfum E, Mantzoros CS. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. Int J Obes. 2014; 38: 1538-1544.
40. Zhao J, Su Z, Qu C, Dong Y. Effects of 12 weeks resistance training on serum irisin in older male adults. Front Physiol. 2017; 8: 171.
41. Chevrel G, Hohlfeld R, Sendtner M. The role of neurotrophins in muscle under physiological and pathological conditions. Muscle Nerve. 2006; 33: 462-476.
42. Lee JH, Jun HS. Role of myokines in regulating skeletal muscle mass and function. Front Physiol. 2019; 10: 42.
43. Clow C, Jasmin BJ. Brain-derived neurotrophic factor regulates satellite cell differentiation and skeltal muscle regeneration. Mol Biol Cell. 2010; 21: 2182-2190.
44. Matthews VB, Åström MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, et al. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia. 2009; 52: 1409-1418.
45. Walsh JJ, Scribbans TD, Bentley RF, Kellawan JM, Gurd B, Tschakovsky ME. Neurotrophic growth factor responses to lower body resistance training in older adults. Appl Physiol Nutr Metab. 2016; 41: 315-323.
46. Forti LN, Van Roie E, Njemini R, Coudyzer W, Beyer I, Delecluse C, et al. Dose-and gender-specific effects of resistance training on circulating levels of brain derived neurotrophic factor (BDNF) in community-dwelling older adults. Exp Gerontol. 2015; 70: 144-149.
47. Roh HT, Cho SY, So WY. A cross-sectional study evaluating the effects of resistance exercise on inflammation and neurotrophic factors in elderly women with obesity. J Clin Med. 2020; 9: 842.

48. Urzi F, Marusic U, Ličen S, Buzan E. Effects of elastic resistance training on functional performance and Myokines in older women—a randomized controlled trial. J Am Med Dir Assoc. 2019; 20: 830-834.
49. Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible neuroprotective mechanisms of physical exercise in neurodegeneration. Int J Mol Sci. 2020; 21: 5895.
50. Pedersen BK. Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol. 2019; 15: 383-392.