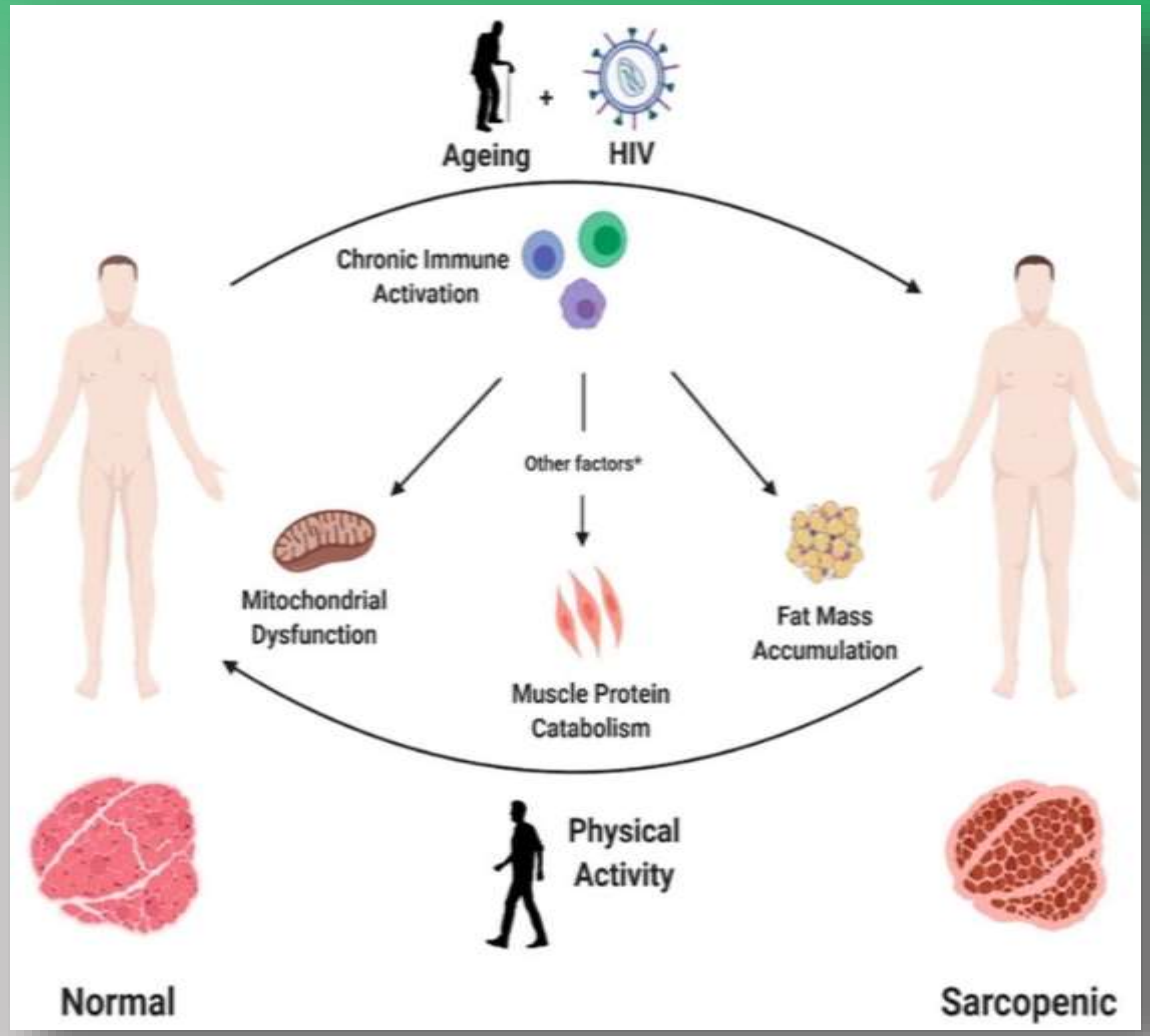
SARCOPENIA and Exercise

SARCOPENIA

- **SARCOPENIA is defined by the progressive reduction of muscle mass, muscle strength and function occurring in the elderly and in people with chronic conditions, such as metabolic syndrome, cardiovascular disease or cancer.**
- **SARCOPENIA started from the age of thirty and from this age our body faces a slow natural loss of muscle tissue. However, this process is accelerated in the elderly and in people with some pathological conditions.**
- **Its prevalence in the elderly population is largely variable, ranging from 5% to 50% depending on age, gender, pathological conditions and diagnostic criteria.**
- **whereas an earlier large survey in New Mexico documented an increased overall prevalence with age, from below 24% in women and men below 70 years of age to >50% in those over 80.**

- **SARCOPENIA is characterized by a progressive loss of muscle fibers that are replaced by adipose tissue, increasing fibrosis and changes in muscle metabolism. Several mechanisms have been suggested to explain how persistent inflammation may lead to these changes in the muscular tissue (Figure 1).**
- **A first potential mechanism involves mitochondrial dysfunction. Immune activation is known to increase reactive oxygen species (ROS) intracellular concentration and cause redox balance disturbances. which, in turn, may lead to mitochondrial DNA damage due to its proximity to freeradical sources and the relative lack of a protein scaold. Consequently, mitochondrial DNA mutations can impair mitochondrial protein synthesis, determining loss of oxidative phosphorylation eficiency and, ultimately, premature cell senescence.**



Sedentary lifestyle is one of the principal causes for loss of muscle mass and strength, which, in turn, determines further reduction of activity levels with further muscle weakness.
In contrast, regular physical exercise is highly effective at counteracting the decline in muscle mass and strength and, possibly, also in reducing the chronic inflammation associated with aging.
Indeed, physical activity represents the most effective strategy in the management of SARCOPENIA in the general population and in specific patient groups.

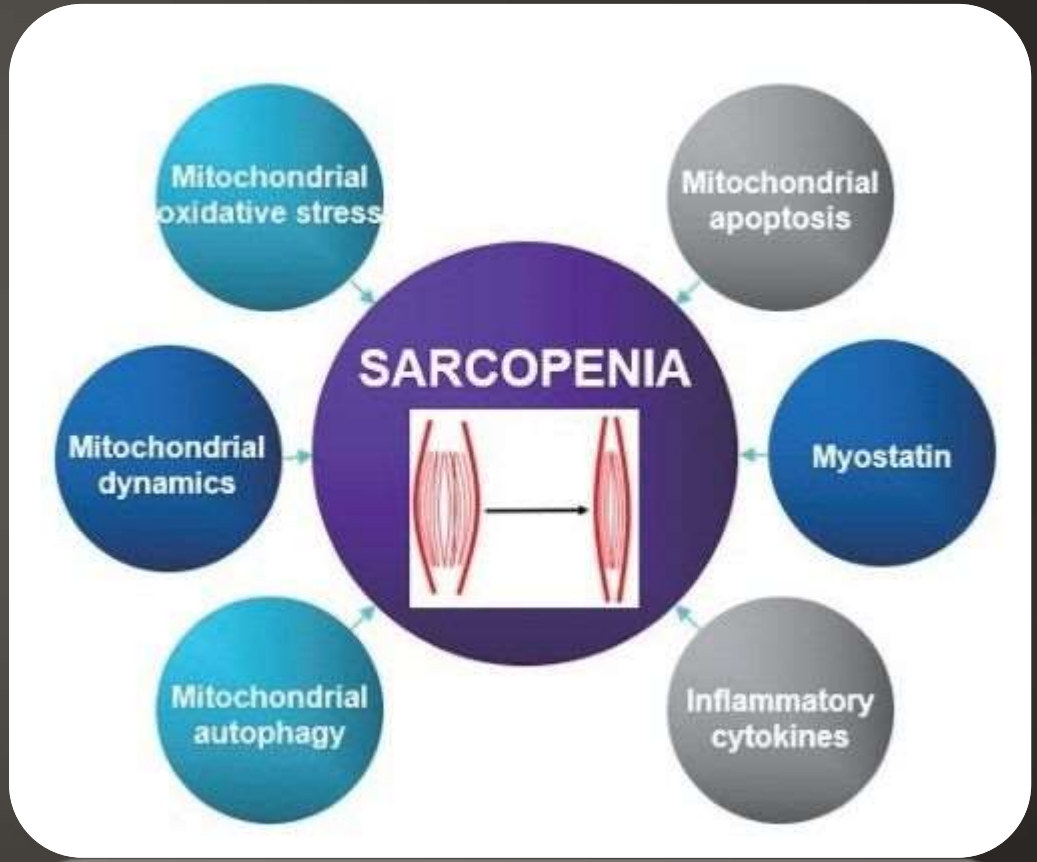
Cardiorespiratory fitness (CRF) reflects the integrated ability of the human organism to transport oxygen from the atmosphere to the mitochondria to perform physical work.
CRF depends on a linked chain of processes, including pulmonary ventilation and diffusion, ventricular function, ventricular–arterial coupling, ability of the vasculature to accommodate and efficiently transport blood from the heart to match oxygen requirements and ability of the muscle cells to receive and use the oxygen and nutrients delivered by the blood.

Many factors responsible for decline of muscle mass:

- It seems that the anabolic potential of skeletal muscle maybe reduced in the elderly
- Insulin resistance/ inflammation/hormonal alterations/perturbation muscle metabolism and decreased muscle proliferation are the main changes involved. Overall the most prominent cause of SARCOPENIA is inactivity . Although it does not completely revert with exercise, the absence of physical activity (PA) enhance muscle mass loss.

POTENTIAL MECHANISMS OF AGE-RELATED SARCOPENIA

A variety of factors and pathways are involved in the pathogenesis of sarcopenia, such as, environmental causes, endocrine problems, motor neuron loss, activation of inflammatory pathways, and reductions in satellite cell counts (Cruz-Jentoft et al., 2010). Moreover, recent research suggests mitochondrial dysfunction and the activation of apoptotic signaling are critical aspects of the pathogenesis of age-related sarcopenia. In this review, we focus on potential causes of age-related sarcopenia. Fig. 1



MYOSTATIN:

MYOSTATIN is an extracellular cytokine and a member of the transforming growth factor β superfamily, playing a negative role in regulating skeletal muscle mass and growth (Elkina et al., 2011). During embryogenesis, MYOSTATIN is exclusively expressed in skeletal muscle and controls the differentiation and proliferation of myoblasts (Elkina et al., 2011) by inhibiting the expression of insulin-like growth factor (IGF-1) or of FOLLSTATIN, which is known to be positively related with muscle hypertrophy.

Furthermore, it has been reported MYOSTATIN is associated with aging. Indeed, YARASHESKI et al. (2002) reported that increases in serum MYOSTATIN levels were highest in physically frail older women and that they were inversely associated with skeletal muscle mass (White and Le BRASSEUR, 2014).

Siriett, et al. (2007) showed that MYO-D and Pax7 (potent markers of MYOGENESIS) protein levels were significantly elevated in gastrocnemius muscles from aged mice treated with a MYOSTATIN antagonist. However, several authors have failed to demonstrate age-related changes in MYOSTATIN mRNA levels in skeletal muscle or in circulating MYOSTATIN-immune-reactive protein levels (White and LeBrasseur,2014). Thus, it seems further studies are needed to resolve conflicting results regarding the relation between MYOSTATIN and aging.

Inflammatory cytokines:

It has been demonstrated inflammatory markers contribute to age-related muscle wasting (BUDUI et al., 2015). For example, elevated levels of tumor necrosis factor alpha (TNF-α) were found to increase muscle catabolism by suppressing the Akt /mammalian target of RAPAMYSIN (m-TOR) pathway (BUDUI et al., 2015).

It also seems inflammatory cytokines may antagonize the anabolic effect of IGF-1 by inducing the development of growth hormone resistance, which decreases both circulating and muscle IGF-1 levels (BUDUIE et al., 2015). However, the effects of these cytokines may be more complex because interleukin 6 (IL-6) may play a role, and it can act as pro- or anti-inflammatory cytokine (Rolland et al., 2008).

Recent experimental studies have suggested that IL-6 in blood can be differentiated from muscle-derived IL-6, which can inhibit TNF-α (Rolland et al., 2008). The involvements of cytokines in SARCOPENIA remain to be clarified, but nonetheless, SARCOPENIA appears to be a cytokine-associated aging phenomenon (Rolland et al., 2008).

Mitochondrial reactive oxygen species & mitochondrial dysfunction

Mitochondrial reactive oxygen species (mtROS) is closely related to oxidative stress in aging skeletal muscle and is a major cause of age-induced sarcopenia.

The accumulation of mitochondrial ROS in aging skeletal muscle leads to tissue degradation, skeletal muscle atrophy, muscle dysfunction, and increases in fibrous tissue (Heo et al., 2017).

mtROS production is associated with mitochondrial DNA (mtDNA) mutations induced by oxidative stress and these mutations result in defective electron transport chain (ETC) components (Alexeyev, 2009).

The incorporations of defective subunits into the ETC disrupts oxidative phosphorylation, reduces ATP synthesis, and further increases ROS production (Alexeyev, 2009). Indeed, Wanagat et al. (2001) reported muscle fibers with mtDNA deletions displayed electron transport system abnormalities and fiber atrophy, and Hiona et al (2010). showed rates of mitochondrial respiration and ATP production were dramatically lower in the skeletal muscles of mt-DNA mutant mice.

Consequently, age-induced mt-ROS, mt-DNA mutation, and mitochondrial dysfunction are considered potential causes of SARCOPENIA (ALEXEYEV, 2009).

EFFECTS OF EXERCISE ON SARCOPENIA

Exercise is essential for health because it increases muscle mass, reduces body fat, and improves muscle strength, endurance, immune function, and the cardiovascular system. Accordingly, exercise should be considered an essential feature of therapeutic strategies targeting age-related sarcopenia. Now I want to briefly describe the effects of aerobic, resistance, and combined exercises on age-related SARCOPENIA.

Aerobic exercise and sarcopenia:

Aerobic exercise causes ATP production in mitochondria within skeletal muscle, and improves aerobic capacity, metabolic regulation, and cardiovascular function.
Furthermore, it contributes to the inductions of mitochondrial biogenesis and dynamics, to the restoration of mitochondrial metabolism, reduces the expressions of catabolic genes and increases muscle protein synthesis (Erlich et al., 2016; Konopka and Harber, 2014; Seo et al., 2016).

Previous studies have shown endurance exercise training may suppress the apoptotic pathway in skeletal muscle and that aerobic exercise helps maintain the expression of autophagy protein and may even increase the expressions of autophagy-related proteins in skeletal muscle (Yan et al., 2012). In addition, several authors have shown aerobic exercise controls mRNA expression of MYOSTATIN (KO et al., 2014).
Given that these molecular factors are associated with age-related SARCOPENIA, it seems aerobic exercise has a protective effect. Indeed, HARBER, et Al (2012) reported that cycle exercise increased muscle size and strength in both 20-years-old and 74-years-old subjects. Moreover, BORI et al. (2012) reported that 12 weeks of aerobic exercise training enhanced mitochondrial biogenesis and mitochondrial fission protein of older subjects. Collectively, aerobic exercise appears to ameliorate mitochondria-related problems and improve muscle hypertrophy and strength. Table 1 summarizes the effects of aerobic exercise on age-related SARCOPENIA.

Table 1. Effects of aerobic exercise on age-related sarcopenia

Subject	Sex	Age	Exercise protocols	Results	References
Rat	Male	28 mo	Treadmill, 3 days, 6 weeks, 60% of VO_{2max}	↑ mTOR levels ↑ Follistatin protein levels = Myostatin protein levels	Ziaaldini et al. (2015)
Mice	Male	17 mo	Voluntary wheel running	↑ Grip strength ↑ Gastrocnemius expression genes (IL-6, Sod1 etc.)	Pence et al. (2016)
Rat	Male	24 mo	Treadmill exercise, 30 min, once a day, 6 weeks	↓ Myostatin mRNA expression ↑ Myocyte proliferation	Ko et al. (2014)
Human	Male/female	65–75 yr	Dance, 60 min for 8 weeks	↑ Muscle mass ↑ Back extensor strength	Chen et al. (2017)
Human	Female	74±3 yr	Cycle ergometer, 3 days/wk for 12 weeks 20–45 min, 60%–80% of HRR	↑ SIRT1, AMPK mRNA expression ↑ Mitochondrial biogenesis	Bori et al. (2012)
Human	Male	74 yr	Cycle ergometer, 12 weeks, 20–45 min, 3–4 day/wk, 60%–80% of HRR	↑ Quadriceps volume (-6%) ↑ Muscle size ↑ Aerobic capacity	Harber et al. (2012)
Human	Female	70±2 yr	Cycle ergometer, 12 weeks, 20–45 min, 3–4 day/wk, 60%–80% of HRR	↑ Aerobic capacity ↑ Muscle size ↑ Muscle strength ↓ FOXO3A, Myostatin, MRF4 mRNA expression ↓ PGC-1α protein levels	Konopka et al. (2010)
Human	Male/female	21–87 yr	Bicycle training, 3–4 days/wk 45 min, 80% peak heart rate	↑ MHC I and MHC IIa mRNA expression ↓ MHC IIx mRNA expression	Short et al. (2005)

↑, increase; ↓, decrease; =, no change; HRR, heart rate reserve; VO_{2max}, maximum rate of oxygen consumption; mTOR, mammalian target of rapamycin; IL-6, interleukin-6; Sod 1, superoxide dismutase 1; FOXO3A, forkheadbox 3A; MRF4, muscle regulatory factor 4; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; AMPK, AMP-activated protein kinase; SIRT 1, sirtuin 1; MHC, myosin heavy chain.

RESISTANCE EXERCISE AND SARCOPENIA :

Resistance exercise is considered an important strategy for preventing muscle wasting because it stimulates muscle hypertrophy and increases muscle strength (Johnston et al., 2008) by shifting the balance between muscle protein synthesis and degradation towards synthesis (Johnston et al., 2008). It is known regular resistance exercise increases the sizes and cross-sectional areas of muscle fibers, especially fast-twitch fibers (types IIa and IIx) rather than slow-twitch fibers (type I) (HEO, et al.2017).

Increases in muscle protein synthesis and muscle fibers hypertrophy increase force-generating ability (Johnston et al., 2008), muscle quality, and physical performance. However, resistance exercise has several limitations. In particular, it has a little effect on the expressions of mitochondrial proteins or their functions, and these are considered potential causes of age-related SARCOPENIA. Nonetheless, resistance exercise is a meaningful exercise prescription for SARCOPENIA in terms of improving muscle mass and function.

Table 2. Effects of resistance exercise on age-related sarcopenia

Subject	Sex	Age	Exercise protocols	Results	References
Rat	Male	30 mo	Stretch-shortening contraction, 2 days/wk	↓ Lipid peroxidation ↓ Oxidative stress levels ~11% ↑ Tibialis anterior muscle mass ~17%	Rader et al. (2017)
Mice	Male/female	15–23 mo	Resistance wheel exercise, 34 weeks	↑ Soleus muscle mass, ↑ Oxidative stress, ↑ Mitochondrial density	White et al. (2016)
Rat	Male	10 wk	4 weeks group, 8 weeks group, Climbing a 1–3 vertical ladder, 10 times, 3 days/wk	4 weeks group: ↑ Mustn1 mRNA expression 8 weeks group: ↑ Mustn1 mRNA expression	Oh et al. (2011)
Human	Male/female	73.6 ± 5.7 yr	RE+LTPA: 12 weeks + 16–18 months	↑ Quadriceps strength (only RE) ↑ Time-up-and-go performance (RE+LTPA)	Geirsdottir et al. (2015)
Human	Male/Female	78 yr	Progressive resistance exercise training (PRT), RE: 3 months of low intensity, 3 months	↑ Maximal voluntary force production for knee extension ↑ Total body FFM = Fat mass	Peterson et al. (2010)
Human	Male	60–70 yr	High and low velocity RE, 2 days/wk for 10 weeks	↑ Arm curling ↑ 30-sec chair-stand ↑ Muscle power	Bottaro et al. (2007)
Human	Male/female	65–78 yr	High-intensity RE, 1–2 weeks/20 weeks, 3 sets of 8 repetitions	↑ Muscle function ↑ Physical performance	Galvão et al. (2005)
Human	Male/female	83 ± 4 yr	PRT ET: 3-month of light intensity, 3-month added RE, 3-month added AE	↑ VO_{2peak} ↑ Physical Performance Test	Binder et al. (2002)

↑, increase; ↓, decrease; =, no change; AE, aerobic exercise; RE, resistance exercise; LTPA, leisure time physical activity; ET, exercise training; FFM, fat free mass; Mustn 1, musculoskeletal embryonic nuclear protein 1; VO_{2peak}, peak oxygen uptake.

Combined exercise and sarcopenia:

- The majority of studies on the effects of exercise have focused on either aerobic or resistance exercise. As mentioned above, aerobic exercise has a little effect on muscle strength or mass compared with resistance exercise (Lee, 2017; TAKASHIMA et al., 2004) whereas resistance exercise can increase the risk of injury, reduce participation rates, and induce boredom because of the extent of repetition (Lee, 2017).
- Also, resistance exercise can be less effective in older individuals because of deficient m-TOR signaling, which is involved in muscle protein synthesis (HEO, et al., 2017).
- Accordingly, no single type of exercise would seem to address adequately the requirements of therapeutic exercise in age-related SARCOPENIA, and thus, it has been recommended well-rounded exercise programs consisting of aerobic and resistance exercises should be preferred (TAKESHIMA et al., 2004). For example, a circuit exercise program has been developed that combines these two exercise types (Lee, 2017; TAKESHIMA et al., 2004).

Recently, Lee et al,(2017) reported that 12 weeks of circuit program improved walking and balancing abilities and isokinetic muscle functions. GUDDLAUGSSON et al, (2013) showed ‘multimodal training interventions’ conducted on 117 elderly subjects for 6 months improved endurance performance as determined by 6-min walking test. Collectively, these reports indicate regular combined exercise can be utilized to combat age-related SARCOPENIA. Further research is needed to determine whether combined exercise retards potential molecular mechanisms of age-related SARCOPENIA. Table 3 presents a summary of the effects of combined exercise on age-related SARCOPENIA.

Table 3. Effects of combined exercise on age-related sarcopenia

Subject	Sex	Age	Exercise protocols	Results	References
Human	Male	69±4.9 yr	1 time for 1 hr, moderated to vigorous intensity for 32 weeks	↑ 6-min walk test ↑ 30-sec chair-stand ↑ Functional reach test	Sousa et al. (2017)
Human	Female	>60 yr	1 time for 50 min, 3 times/wk, AE: treadmill, RE: knee flexion, arm raise, squat for 12 weeks	↑ Lean mass, ↓ Body weight, ↓ Body fat	Bocalini et al. (2012)
Human	Male/female	71–90 yr	AE of 5 day/wk, RE of 2 day/wk for 6 months	↑ Shorts physical performance battery ↑ 8 foot up and go test	Gudlaugsson et al. (2013)
Human	Male	40–67 yr	CE: 4 times/wk for 21 weeks	↑ Maximum strength = type II muscle cross-sectional area	Karavirta et al. (2011)
Human	Female	50–65 yr	3 times/wk, 50%–75% of 1 repetition maximum for 12 weeks	↑ Growth hormone ↓ Body fat ↑ Metabolic-syndrome factors	Seo et al. (2010b)

↑, increase; ↓, decrease; =, no change; AE, aerobic exercise; RE, resistance exercise; CE, combined exercise.

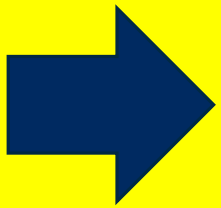
RET AND THE MANAGEMENT AND PREVENTION OF MUSCLE WASTING AND WEAKNESS:

While SARCOPENIA and DYNAPENIA are realized to be major clinical problems for older adults, until recently there has been little wide spread support for ways to combat these debilitating conditions. However, research on the effects of exercise and nutrition on SARCOPENIA and DYNAPENIA has rapidly expanded in the past one to two decades (SAYER et al., 2013). Today, there is still limited evidence suggesting that pharmacologic interventions effectively ameliorate SARCOPENIA and/or DYNAPENIA However, there is strong and growing evidence that progressive RET can combat both SARCOPENIA and DYNAPENIA (Burton & SUMUKADAS, 2010), as RET has a profound effect on virtually all of the physiological mechanisms in the nervous system and the muscular system known to influence strength (DUCHATEAU & ENOKA, 2002; Russ, Gregg-Cornell, Conaway, & Clark, 2012).

For instance, maximal motor unit discharge rates, a key 'neural factor' involved in muscle strength, increased 49% in older adults following only 6-weeks of high-intensity progressive RET (KAMEN & Knight, 2004). Non-mass dependent muscular factors, such as muscle fiber fascicle length and tendon stiffness, have also been observed to increase (10% and 64%, respectively) following RET in older adults 64%, respectively (Reeves, MANGANARIS , & NARICI , 2003). Additionally, RET is also a powerful stimulus for inducing muscle hypertrophy as illustrated by 24-weeks of RET, when coupled with modest protein supplementation, increasing thigh muscle cross-sectional area 4.6% in mobility limited older adults (CHALE et al., 2013). Given that there exists widespread evidence that inactivity, which is prevalent in the elderly (TROIANO et al., 2008), leads to loss of muscle mass and strength (Clark, 2009), findings of this nature would (or should) lead all scientists and clinicians to support the use of RET for treating, slowing, and/or preventing SARCOPENIA and DYNAPENIA.

CONCLUSIONS:

1. **MITOCHONDORIAL OXIDATIVE-STRESS**
2. **APOPTOSIS**
3. **DAYNAMICS**
4. **MITOPHAGY**
5. **MAYOSTATIN**
6. **INFLAMMATORY CYTOKINES**



are all believed to be associated with age-related SARCOPENIA.

Nevertheless, aerobic, resistance, and combined exercise training regimes have been shown to produce the most beneficial preventive and therapeutic effects. Further research is required to elucidate the cellular and molecular mechanisms responsible for protective effect of regular exercise training on age-induced SARCOPENIA of skeletal muscles

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Thanks For Paying Attention