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Review Article

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Changes in muscle mass and strength after menopause

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Abstract

Menopause is associated with a natural decline in estrogen, that increases visceral fat mass, decreases bone mass density, muscle mass, and strength. This review will examine the role of menopause transition and associated decrease in hormonal status with regards to those changes. We will also overview the efficiency of physical exercise and nutrition on muscle subcharacteristics. Studying changes in muscle mass associated with menopause is important, because of the high number of postmenopausal women in developed countries and the related risk of physical incapacity. Among modifiable factors, low physical activity and protein intakes are the best contributors to sarcopenia and the loss of strength in postmenopausal women. On the other hand, some biological factors, namely oxidative stress, inflammation, estrogen and other hormone deficiency are predictors of these phenomena. Interestingly, some methods have the potential to attenuate the loss of muscle mass and strength such as exercise, and supplement intake.

Keywords: Postmenopausal Women, Exercise, Sarcopenia, Nutritional Supplements

Introduction

Since the 1960's, there has been a slow but constant rise in the number of elderly people in the population. With the aging of baby boomers and the ongoing increase of life expectancy, North America will see a steep increase of the elderly population in the coming years[1]. In 2005, one out of ten persons was 60 years and older, and the United Nations predicts that one person out of five will be 60 years or older by 2050.

Aging is associated with a natural decline in physiological functions, including a loss of bone mass density (BMD)[2], muscle mass[3] and strength[4]. Overall, the decline in muscle mass averages 0,4 to 0,8 kg per decade, starting at the age of 20 years old[5]. However, this diminution is not linear and does not occur at the same rate and age in both sexes. In fact, it has been proposed that, in women, an accelerated loss of muscle mass and strength occurs at an earlier age than in men, around the time of menopause[4,6-9], possibly making them weaker at 65-69 years old than men aged 85-89 years old[10]. The decrease in estrogen occurs at a mean age of 51 yrs in Canada[11] and life expectancy is higher for women (80 yrs) compared to men (73 yrs)[12]. This means that women spend more than 30 years in postmenopausal status. Hence, there is growing interests in studying the effects of the deficit in estrogen in postmenopausal women's physical health and function.

A good body of evidence supports that the decline in muscle mass may be in line with the decrease in estrogen that characterizes menopausal years. The decrease of estrogen contributes to the loss of BMD, the redistribution of subcutaneous fat to the visceral area, the increased risk of cardiovascular disease and the decrease in quality of life[13]. To exacerbate the negative impact of menopause on women's health, the drop in estrogen may also have a direct effect on muscle tissue[6,8,14-19].

This review will examine the role of menopause transition and associated decrease in hormonal status with regards to muscle mass, strength, and other subcharacteristics of muscle tissue in humans and animals. In addition, we will report on the new evidence regarding the presence of estrogen receptors in human muscles. Lastly, the potential effects of exercise and hormone-replacement therapy (HRT), isoflavone supplementation (alone or in combination with exercise) or vitamin D on muscle mass and strength of postmenopausal women will be addressed.

Methods

For the purpose of this review, we performed a search on Pubmed and Medline databases. Keywords used were: menopause, muscle mass, sarcopenia, muscle function, estrogen

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and muscle strength. To be included in the review, an article had to address the relation between muscle mass or muscle tissue subcharacteristics and estrogen or menopause in humans or animals.

Changes in muscle mass and tissue subcharacteristics after menopause

It is well established that aging is associated with a decline in muscle mass[4], called sarcopenia[10]. Sarcopenia is clinically defined as 2 standard deviations below the mean appendicular muscle mass of young healthy adults of a reference population[5]. It is related to limited functional performance and physical disability[20] and women are more susceptible to present these health problems, as compared to men, because they live longer[3]. This muscle loss is primarily due to a imbalance between muscle protein synthesis and muscle protein breakdown[21], and the increase of catabolic factors such as oxidative stress and inflammation[10]. In addition, other factors such as menopause-associated decline in hormonal levels are thought to be implicated in this process.

Muscle mass in women tend to decrease gradually after the 3rd decade of age, and shows an accelerated decline after the 5th decade[22]. A cross-sectional study by Rolland et al[23] showed a decline of 0.6 % per year of muscle mass after menopause. Accordingly, total body potassium, a marker of lean body mass, has been shown to decrease significantly during the first 3 years of menopause[22]. In this regard, the prevalence of sarcopenia in the New Mexico elderly study population by Baumgartner et al[20] was shown to be approximately 23.6% in healthy independent postmenopausal women (<70 years old) as compared to 15.4% in men (<70 years old), supporting that sarcopenia is still increasingly present in men but especially in postmenopausal women. However, the study of Tanko et al[24] demonstrated that muscle mass is negatively correlated with age and it remains difficult to establish the relative contribution of menopausal transition as opposed to age with regards to the loss of muscle mass, especially since the loss of muscle mass is influenced by many confounding factors, such as low physical activity[25], inflammatory factors[26], leg strength and power, and BMI[27] that are all simultaneously related to age and menopause status. Although longitudinal studies are needed to determine the relative contribution of age and menopause-related drop of estrogen in the onset of sarcopenia, more and more cross-sectional studies are available to support a correlation specifically between muscle mass subcharacteristics and estrogen metabolism.

Changes in muscle composition after menopause

Although the literature pertaining to changes in muscle mass due to menopause *per se* is not abundant, some have investigated changes in subcharacteristics of muscle tissue during menopause. In this sense, it was shown that women aged 65-80 years old have twice the amount of non-contractile muscle tissue per unit of muscle cross-sectional area (CSA) as compared to younger women aged 23 to 57 years old[28]. This is supported by the fact that non-contractile tissue, such as intramuscular fat, is significantly increased after menopause[29]. These are in agreement with Brown[30], who explains that women store fat in the muscle because they utilize more fat than glycogen as fuel, compared with men. Lipoprotein lipase (LPL) is responsible for utilizing triglycerides in muscle and plays a crucial role in lipid metabolism and lipid transport[31]. With aging and physical inactivity, there is a decrease in the activity of LPL enzymes in muscles[32], which could lead to an increase in intramuscular fat storage. Furthermore, it seems that estrogen also have independent effects on LPL enzyme. In fat tissue of premenopausal women, LPL increases the storage of fat in the gluteo-femoral area and inhibits fat storage in the abdominal region[33-35]. However, after menopause, women did not display regional differences in fat storage, suggesting that LPL activity is increased in both abdominal and gluteal region[36]. In other words, it can be assumed that postmenopausal women not undertaking HRT maintain their ability to store fat under the form of muscle triglycerides but lose their ability to oxidize it, thus leading to an excess accumulation of fat storage under the form of intramuscular fat. In addition, the "protective effect" of estrogen on abdominal fat storage is weakened. Unfortunately, this is likely to lead to a diminution of insulin sensitivity and a higher risk for postmenopausal women to have type II diabetes[37].

Factors contributing to the decline in muscle mass in postmenopausal women

In postmenopausal women, some important factors contribute to the decline in muscle mass. It seems that physical inactivity, protein intake and oxidative stress[38] contribute the most to sarcopenia in postmenopausal women[39,40]. In addition, new data is demonstrating that vitamin D might also have a role on muscle function[41]. Although these factors are not specific to menopause, several studies support that they are exacerbated by changes in this status[6,8,14-19]. Moreover, sex hormones, such as estrone, estrogen and other factors such as growth hormone (GH), dehydroepiandrosterone (DHEA), insulin-like growth factor-1 (IGF-1) and insulin appear to be correlated positively with muscle mass[3,8,40,42].

First, physical activity, especially resistance training, is a major determinant for maintaining muscle mass and reducing the accumulation of intramuscular fat mass. In a longitudinal study of 9 years by Hughes et al[43], high physical activity level was shown effective in decreasing body weight, although it was not sufficient to completely prevent the decline in muscle mass. However, physical activity was reported as «sports and recreational activity» and thus included all types of activities (aerobic and resistance regardless of intensity). In agreement, Klitgaard et al[44] showed that men who were endurance athletes had the same lean mass and muscle strength as their sedentary aged-matched controls. Nonetheless, the same authors reported that master athletes who were weightlifters had the same muscle structure as men in their twenties[44]. Accordingly, Pollock et al[45] showed that older individuals who had maintained regular participation in resistance training preserved higher levels of muscle mass as compared to sedentary or endurance-trained

counterparts. In view of that, Bouchard et al[46] conducted a resistance training program in 48 obese postmenopausal women (55-75 years old) not taking HRT for 12 weeks and concluded that resistance training alone (versus caloric restriction alone and combined with resistance training) increased their physical capacity score. Hence, while endurance exercise might not be highly efficient at preventing sarcopenia on a general standpoint, resistance exercise may be the key strategy to maintain muscle mass in postmenopausal women[47].

Protein intake is important for postmenopausal women, especially under the form of essential amino acids. The current recommended dietary allowance of daily protein intake is 0.8 g per kilogram of body weight in younger and older men and women[48]. This is considered as the minimum to maintain the balance between protein synthesis and breakdown. Nevertheless, there is evidence that this recommendation may not be suitable for elderly people. In a recent review by Wolfe et al[49], 1.2 g/kg seemed more adequate and safe for older men and women alike. Recently, Bopp et al[50] studied the effects of a dietary modifications combined with exercise in obese postmenopausal women not on HRT. Their results after a 20 week-intervention showed that women who had a high protein intake (0.8 g/kg) lost less lean mass compared to their counterparts with a low protein intake (0.47 g/kg). Nevertheless, given the fact they only had a protein intake of 0.8 g/kg, it is albeit difficult to know if a higher protein intake could totally prevent the loss of muscle mass, and it would be interesting to study the effect of a higher protein intake (such as 1.2 g/kg) in the same population. The same study showed that for an increase of 0.1 g/kg of daily protein intake, the drop in muscle mass was reduced by 0.62 kg. Interestingly, we showed that the consumption of proteins from healthy animal sources (that are rich in essential amino acids) is associated with muscle mass in elderly women[51]. Altogether, these strongly support that adequate protein intake (amount and types) is essential to prevent or, at least, retard sarcopenia. It is important to note that these recommendations of essential amino acids and protein supplementation are not exclusively for postmenopausal women. In older men, an adequate consumption of animal proteins is as important as for women. However, since women have significantly lower muscle mass than men[52], they may be more at risk of protein imbalance. Therefore, having a balanced diet with a higher intake of animal proteins could reduce the loss of muscle mass in postmenopausal women.

With menopausal transition, there is an increase in oxidative stress marked by the imbalance between the production of free radicals and the destruction of these free radicals through an inadequate antioxidant system[38,53]. Oxidative stress is related to a higher reactive oxygen species production from the mitochondria, which in turn provokes cell apoptosis[54]. The vicious cycle theory[55] proposes that mitochondrial DNA is damaged by oxidative stress, affecting the capacity of producing energy from the electron transport chain. The reduced capacity of the mitochondria to produce energy makes it more susceptible of apoptosis which finally provokes muscle fiber atrophy or death, eventually leading to sarcopenia. Noteworthy, the decline in IL-6 and TNF-α have also been shown to increase the risk of physical disability[56]. Signorelli et al[38] found that postmenopausal women (age range 45-55 years old, not on HRT) had significantly higher oxidative stress marker levels and a lower antioxidant capacity, compared to premenopausal women (30 to 35 years old). One reason that can explain the increase in oxidative stress in women is the fact that they display a significant weight gain during menopausal transition[57]. Mittal et al[58] confirmed the correlation between oxidative stress and body weight, concluding that women who had a higher body weight had a enhanced oxidative stress level[58]. Another hypothesis is that estrogen may play a protective role against oxidative stress, although implied mechanisms are not clearly understood[59].

Furthermore, vitamin D is known to play a primordial role in the regulation of calcium and bone development and maintenance[60]. Vitamin D is produced mainly by the skin and can be affected by age, latitude, time of day, season of the year and pigmentation of the skin[61]. In addition, there is new evidence that vitamin D has an association with muscle function. To support this association, Zanello et al[62] and Bischoff et al[63] identified vitamin D receptors on muscle cells. Interestingly, physical performance and vitamin D have been shown to be correlated together in the NHANES III survey where men and women aged 60 years and older who had high serum 25 (OH)D levels (>94 nmol/l) had better results (8-foot walk test and get chair stand) than subjects with lower levels (<60 nmol/l)[64]. Moreover, some authors found a positive association between grip strength and serum 25 (OH)D levels[65]. It has even been demonstrated that lower levels of 25 (OH)D (under 25 nmol/L) had an increase risk of falling in the Longitudinal Aging Study Amsterdam[66].

The implication of vitamin D on muscle performance seems to be at the muscular cell level and structure. In this regard, vitamin D deficiency in adults was shown to be implicated in the atrophy of type II muscular fibers[67]. Additionally, an increased infiltration of fat between muscle fibers and enlarged interfibrillar spaces with vitamin D deficiency was reported[65]. One would thus suggest that vitamin D plays a crucial role in the maintenance of type II fibers and preventing falls. Based on these assumptions, Pfeifer et al[68] concluded that postmenopausal women (mean age 74 years old) undertaking vitamin D with calcium supplementation improved their body sway and gait performance compared to a group who only took calcium supplements.

Vitamin D supplementation seems to be important not only to maintain BMD, but also muscle function and strength, therefore attenuating the risk of falls and the loss of balance. This topic, obvisouly deserves further investigation.

Among biological markers associated with muscle mass loss, DHEA is a prohormone that can transform into sex steroids, such as androgens and estrogen. DHEA has many important roles in the human body as it may contribute to the increase in muscle mass, the improvement in glucose and insulin levels, the decrease in fat mass and reduce the risk of breast cancer[69]. Circulating DHEA seems to decline with age, especially at menopause for women. As such, a steep decline seems to occur between peri-menopausal women and postmenopausal status[70].

Among other things, it has been demonstrated that a low concentration of DHEA is associated with decreases in muscle mass and physical performance[69,71].

GH also regulates whole body composition and growth during the developmental period of children, exerting an anabolic effect on muscle and bone tissues[72]. Circulating levels of GH seem to remain stable throughout adult life followed by a decline at menopause[73]. In fact, lower 24-h concentrations of GH have been observed in postmenopausal women (58-70 years old) compared to women who were still premenopausal (45-51 years old)[74] (1.0 vs. 1.8 mU/L) and estradiol was correlated with GH concentrations[75]. This decrease in GH is likely to accelerate the loss of muscle and bone mass density[72] and has been shown to potentially lead to a gain in intra-abdominal fat[76].

IGF-1 is a protein that activates muscle protein synthesis and inhibits muscle protein degradation[77]. It is mediated by growth-hormone releasing hormone (GH-RH) and works in pair with GH[73]. Serum IGF-1 is produced primarily by the liver and its levels are more stable than GH[78]. The effect of IGF-1 is mainly on the PI3K/AKT pathway which is also activated by exercise[78]. Noteworthy, the PI3K/AKT pathway holds two types of receptors; insulin receptors (IR) and IGF-1 receptors, explaining why both insulin and IGF-1 can promote muscle protein synthesis[78]. IGF-1 and estrogen has been shown to decrease with menopause[79], thereby augmenting pro-inflammatory cytokine levels such as IL-6 and TNF-α[80,81]. Elevated levels of these cytokines were shown to contribute to sarcopenia[56,82-84], and increase the risk of physical disability[56] through their role in muscle protein breakdown[85]. Hence, the diminution of IGF-1 levels and the loss of the protective effect on circulating cytokines of estrogen during menopause[59] could accelerate the loss of muscle mass.

Impaired insulin sensitivity has also been proposed to influence muscle mass in postmenopausal women. Insulin is an anabolic hormone that inhibits muscle protein breakdown and promotes synthesis[86], thus playing a crucial role in favoring muscle anabolism[87]. Chevalier et al[86] demonstrated that obese postmenopausal women (67-71 years old) have a reduced capacity of protein anabolism, because of their higher insulin resistance. A further study by Chevalier et al[87] demonstrated that aging conducted to a reduced capacity of the anabolic response of protein following amino acid infusion. This supports the decrease in the efficacy of insulin to stimulate muscle protein synthesis[87]. It has also been shown that the suppression of protein breakdown by insulin is impaired in older adult[88]. Although the underlying mechanisms are not completely understood, a greater adiposity in postmenopausal women may explain the blunted protein metabolism[87]. However, no studies have addressed the specific relationship between protein metabolism and estrogen levels before or after menopause.

As a final point, the decline in muscle mass with aging is inevitable, be it due to age or menopause. It is quite difficult to discriminate between the effects of aging and menopause, as both take place simultaneously. A low physical activity is related to an accelerated loss of muscle mass, and protein intake (>0.8 g/kg/day mainly from essential amino acids) is important to maintain muscle mass by promoting an increase in muscle protein synthesis and blunting protein breakdown[50]. With menopausal transition, the decrease of estrogen seems to be related with an increase in oxidative stress. Insulin sensitivity, circulating DHEA, GH, IGF-1 and vitamin D all appear to be decreased after menopause and all seem to be related in some ways with the loss of muscle mass in women. Therefore, all of these are directly or indirectly considered as implicated in the pathogenesis of sarcopenia in postmenopausal women. Fortunately, it appears that resistance training can contribute to a healthy lifestyle in postmenopausal women and retard sarcopenia, likely preventing its associated decline in physical function[89-91].

Changes in muscle strength after menopause

It is well established that aging is related with the loss of muscle strength, and this loss is partly related to sarcopenia[3]. The decrease in muscle strength can play a detrimental role in physical function impairments[92-95], such as rising from a chair[96], walking speed[92], climbing stairs[97] and the capacity to recuperate after a loss of balance[98].

Women tend to lose muscle strength around the 5th and 6th decades of age[8,18]. As such, some studies showed that women experience a 21% decrease in strength between the age of 25 and 55 years[99]. As with muscle mass, the loss of muscle strength appears to be concurrent with the occurrence of menopause[6,8,14-19]. This section will overview some of the factors contributing to the decrease of muscle strength resulting from menopause and the respective role of strength parameters (isokinetic, isometric and power output) on functional performance in postmenopausal women.

The loss of estrogen and muscle strength

Some authors suggested that the loss of muscle strength coincides with the estrogen deficit of menopause[6,8,14-18]. Although the mechanisms that lie beneath are not clearly understood, some studies show a correlation between muscle strength and circulating estrogen levels[8,100]. It is proposed that estrogen has an anabolic effect on muscle by the stimulation of IGF-1 receptors[101]. In addition, there is some evidence that estrogen receptors (ER) are present in human muscles (expressed at mRNA level)[102], under the form of ERα and ERβ in the nuclei of muscle fibers and capillaries[103]. Interestingly, it has been shown that the number of ERs on muscle fibers is greater in men, women and children, as compared to postmenopausal women[103]. Noteworthy, estrogen receptors are not only dependent on circulating estrogen to be activated but IGF-1 can also activate the transcriptional activity of estrogen receptors[104,105]. Hence, estrogen receptors could play their role on muscle strength through the action by both estrogen and IGF-1. Nonetheless, both estrogen and IGF-1 drop at menopause, which is likely to affect muscle mass and strength.

However, Bassey et al[106] found divergent results on the effects of estrogen on muscle strength. After evaluating handgrip strength, leg extensor power and isometric strength in 264 men

and 229 women (89 premenopausal, 92 menopausal not on hormonal therapy, 15 on hormonal therapy and 33 perimenopausal), they concluded that there was no difference in strength and leg extensor power between women of different hormonal status. In accordance, a study conducted in young females undergoing *in vitro* fertilization, displaying reduced levels of estrogen, found no protective effect of estrogen on muscle strength[107]. However, it is possible that estrogen does not have the same physiological effect in younger (mean age 34 years old) than in older women and it is thus hazardous to generalize to the postmenopausal population. Another study from Humphries et al[108] supported the idea that there is no relationship between circulating estrogen and muscle strength, by comparing four groups of women of different ages (45-49, 50-54, 55-59 and 60-64 years old) taking HRT and not. The authors concluded that it was the effect of age and not estrogen deficit that promotes the loss of muscle strength. Nevertheless, some suggested that it may not be estrogen that plays a role on muscle strength but rather progesterone alone or the combined with estrogen[107].

Hence, the effect of menopause on muscle strength is not well established. More research is necessary to elucidate the potential effect of estrogen on muscle mass and its exact role as opposed to the role of progesterone or age. As of now, it is difficult to draw a definit conclusion because of the use of different muscles, the differences in age of subjects and, when appropriate, the length of HRT use. Interestingly, muscle fiber type distribution changes that can be observed in postmenopausal women have not been controlled for and may partly explain these discrepancies.

Fiber type distribution

There is an atrophy and denervation of type II fibers and a re-innervation of those fibers with axons from type I motor units that coincides with aging[10], rendering older individuals weaker and slower[109]. Evidence also shows a motor unit firing irregularity that can play a part in the diminished capacity of developing strength and power[110]. This is in agreement with Stanley et al[9], who showed a decrease in power output and in the ratio between flexor and extensor strength in aging women, suggesting that this decline may be due to a type II fiber loss. In a cross-sectional study on women by Widrick and colleagues[111], it was found that type I muscle fibers presented a larger cross-sectional area than type II fibers, independently of HRT status. To our knowledge, this is the only report that compared muscle fiber characteristics between postmenopausal women taking HRT or not. Although these changes are not specific to postmenopausal women, they are observed in that population and more research is needed to evaluate muscle fiber changes during the loss of estrogen in postmenopausal women. It has to be noted, however, that the estrogen receptors found in muscle tissue seem to be expressed more specifically on type II muscle fibers[30]. As mentioned above, type II fibers are reduced in number and size in postmenopausal women[111]. Therefore, we hypothesize that estrogen replacement would not result in increases in muscle strength because of the reduced number of ER receptors in postmenopausal women.

Based on these results, it remains difficult to establish a direct relationship between menopausal status and muscle fiber type distribution in women and the role of hormones on muscle fibers is still poorly understood. Obviously, this question deserves more attention, especially since type II muscle fibers are important to produce fast and strong contractions[112] and for being capable of completing tasks of daily living[113].

Contractile properties

Although not studied in humans, there is some intriguing evidence on the loss of estrogen in mice that contribute to generate hypothesis as to the role of estrogen for muscle contractile properties. Wohlers et al[114] studied the contractile properties of ovariectomized mice muscle, showing they have less capability of activating AMPK phosphorylation. In fact, among physiological processes affected with a decrease in female hormones, there is some evidence that AMPK activity is altered[115-117]. The adenosine monophosphate kinase (AMPK) protein is necessary for glucose uptake[118] and lipid oxidation in muscle[119]. Hence, it is highly implicated in the production of energy that is needed to produce muscle contractions. D'Eon et al[116], also showed that estradiol activates AMPK in mice muscles in the presence of elevated concentrations (10 μmol/l). At the opposite, AMPK is inhibited when all estradiol is metabolized into its inactive form. Hence, we can speculate that menopause could reduce the phosphorylation of AMPK and alter glucose uptake and lipid oxidation in skeletal muscles suggesting that exercise (repetitive contractions) is important for maintaining muscle metabolism and contractile properties. The reduced capacity of muscle to metabolize triglycerides may partly explain in part the increase in fat mass[120] and insulin resistance[37] during menopause. This, however, remains to be demonstrated in humans.

Power output, maximal, isokinetic and isometric force in postmenopausal women and elderly women

Some studies suggest that power is more important than isometric strength for completing activities of daily living[14], such as recovering from a loss of balance[98], rising from a chair[96] and climbing steps[97] and that power decreases more than isometric strength with aging[19,92]. Other decreases in muscle characteristics are a loss of torque at high velocity (120, 180 and 240°/s) and decreases of isokinetic strength of approximately 10 N/year for postmenopausal women[28].

These losses in isokinetic force and power output can be explained mostly by neurological factors. At first, there is a reduction of functional motor units, which is especially noticeable around 60 years old[136]. This has been related to the loss of muscle strength in older women[137]. Even more, it has been suggested to be the most important factor that contributes to sarcopenia and muscle weakness[136]. In addition, as mentioned earlier, there is inevitably a loss of type II fibers with aging[138]. Meanwhile, there is evidence of re-innervation of type II fibers with type I motor units[10] which could explain the reduced capacity of maximal strength in postmenopausal

women. Moreover, there is also a drop of calcium release by the sarcoplasmic reticulum reported by Delbono et al[139]. The drop of calcium release explains the reduced capacity of forming actin/myosin bridges. Finally, a change in the ability to recruit all of the motor units leads to a decrease in force per unit of cross-sectional area[140].

It can be hypothesized that estrogen has a protective role on muscle power through its action on type II muscle fibers[30] such as discussed above. It has also been suggested that estrogen may affect the central nervous system[141], by playing a role on fine motor skills[142] and coordination[143]. This assumption is supported by a study from Carville et al[14] showing that postmenopausal women taking HRT were protected against the loss of power output but not isometric strength. This may take place through an implication of the central nervous system[141]. These results are in agreement with other studies concluding that HRT has a protective role on muscle power[8,19,28,144]. The mechanism of HRT or an elevated concentration of estrogen (such as in premenopausal women) remains to be determined.

To conclude, power output appears to be the most important factor in the context of performing daily activities[95]. In this sense, maintaining muscle strength and, especially, power output, is instrumental in the quality of life of older postmenopausal women[14,92]. As such, women, who tend to have a more important postural instability, may need power and high velocity strength to protect themselves from falls[145] which can increase the risk of fractures[146], especially after menopause, because of the decrease in bone mass density[147].

The effects of exercise and hormone replacement on muscle mass and strength

The importance of muscle strength in everyday life commands to examine efficient strategies to prevent its loss. Evidence suggests that resistance exercise and proper nutrition are important to maintain or prevent the accelerated loss of muscle strength due to aging and, potentially, menopausal status. Replacement therapy may be also be indicated.

Hormone replacement therapy (HRT) is considered as a potential strategy to play a protective role on muscle strength and power[8,14,16,17,19], although contradictory results have also been reported[106,107]. Noteworthy, HRT has been demonstrated to produce greater risks than benefits for the health of postmenopausal women with a history of heart disease[121]. In addition, Rossouw et al[121] found significant risks for breast cancer, colorectal cancer, stroke and cardiovascular diseases. Although Phillips et al[122] showed that women undertaking HRT early after menopause had no detriment effect on cardiovascular risk, and that women starting HRT later in menopause have a significant higher risk of cardiovascular diseases. However, newly published data from the Women's Health Initiative[123] demonstrated that the timing of HRT does not influence the risk of cardiovascular disease, breast cancer and venous thromboembolism. As of now, using low-dose HRT for the relief of certain menopausal symptoms, as long as its use is reviewed every 3 to 6 months[124], seems to remain pertinent but study results may not support using HRT specifically for maintaining muscle strength after menopause.

One alternative approach to HRT in postmenopausal women is phytoestrogen supplements. Isoflavone supplements, which seem to be the most important on preventing disease, are found in soy beans, legumes and soy bean products[125] and they are structurally similar to the human hormone oestradiol. Aubertin-Leheudre et al[126] studied the effects of 70 mg/day of soy isoflavone supplementation for 24 weeks on muscle mass in obese-sarcopenic postmenopausal women and found that women significantly increased lean mass and muscle mass. One potential mechanism is that isoflavone supplementation may attenuate the high concentration of pro-inflammatory markers that contributes to muscle protein breakdown[59]. Those promising results lead us to conclude that this alternative strategy combined with strength training might be beneficial for postmenopausal women. More research is thus needed to establish a direct relationship and propose efficient strategies to maintain muscle strength and mass in postmenopausal women.

It has to be kept in mind, however, that older women have a decreased amount of contractile protein per cell unit, especially in type II fibers[127]. Because estrogen receptors can help the repairing process after strength training[128] and are more numerous on type II fibers[30], it is proposed that the loss of type II fibers after menopause might amplify muscle protein breakdown and could lead to a reduction of the response to muscle adaption response after exercise. However, many questions remain as to the role of these receptors in muscle mass anabolism, or their affinity with IGF-1[104].

Another prospective approach might be hormone replacement other than estrogen such as DHEA. The impact of DHEA supplementation on muscle mass is not yet clear in postmenopausal women. One study demonstrated positive effects of a 12-month percutaneous administration of DHEA on muscle mass in 15 postmenopausal women[129]. However, many studies demonstrated negative results of an administration of DHEA alone[130-132]. Yet, there seems to be evidence of a beneficial effect of weight-lifting exercise combined with DHEA supplementation to increase muscle mass and strength[130]. In contradiction, a study by Igwebuike et al[133] examined the combination of a 12 week exercise program (resistance and aerobic) and DHEA supplementation on muscle mass and showed that DHEA supplementation did not increase the gains of muscle mass induced by the exercise program. Since the intervention was shorter than Diamond et al[129] study, one might consider that DHEA can only have effects following long-term supplementation. On the other hand, GH supplementation has been studied as to its effect on muscle mass in older women. Two review articles seem to agree on the lack of an effect of GH supplementation in elderly individuals for increasing GH concentration back to the levels of young adults[134,135]. Fanciulli et al[135] suggested that exercise can be a more efficient method for increasing GH secretion in postmenopausal women but these matters need more attention before they can be taken seriously. Hence, as of now, the use of DHEA or GH replacement as a strategy against muscle mass and strength decline has not produced conclusive results.

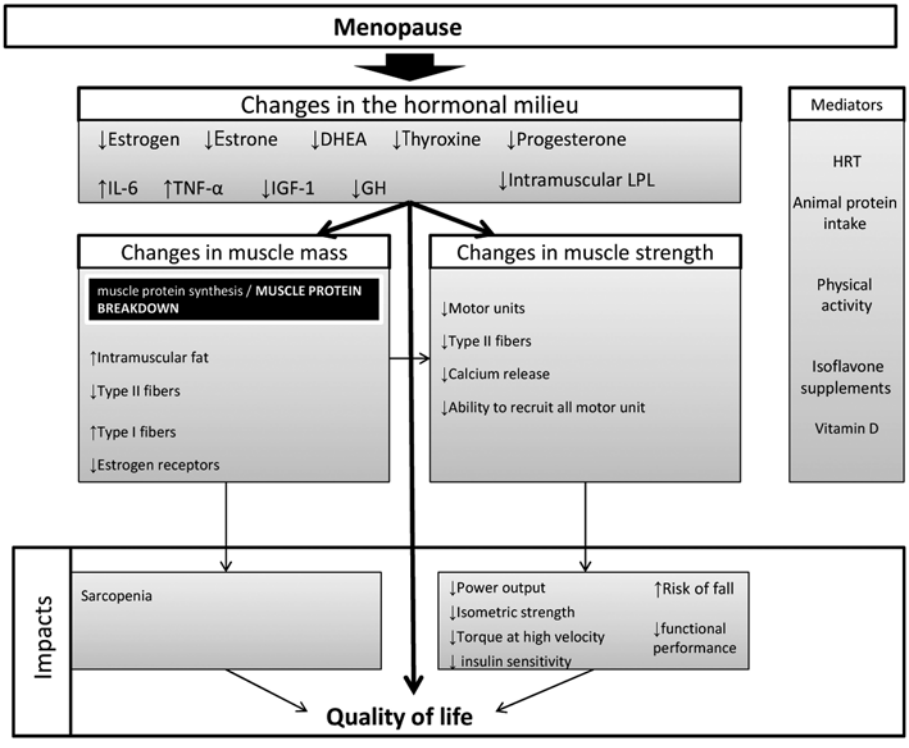

Figure 1. Menopause-related changes on muscle mass and its impacts on different characteristics that contribute to quality of life.

Conclusion

Menopausal transition is associated with a decline in estrogen, GH, IGF-1, and DHEA, a decrease in muscle protein synthesis, and an increase in catabolic factors such as inflammation. More importantly, low physical activity, protein intake and elevated oxidative stress are the greatest contributors of sarcopenia in postmenopausal women. The low concentration of estrogen seems to be related with a decline of muscle mass and muscle strength, but the conflicting results among studies make it difficult to establish a formal relationship. Nonetheless, some studies support the presence of estrogen receptors on muscle tissue, especially on type II muscle fibers. Although their roles are not completely elucidated, these receptors might contribute to the synthesis of muscle tissue at rest and the repairing process of muscle fibers after exercise. Simultaneously, the loss of muscle strength may also be related to menopausal status. While muscle strength is known to play an important role in functional performance and quality of life, the decline in power output is the most important factor of muscle strength and function in postmenopausal women, contributing to the risk of falls and fractures.

It is albeit difficult to differentiate between physiological changes that are solely due to age as opposed to those related with menopause. It remains certain, though, that muscle mass and strength decrease in older women, be it due to menopausal status or age. Some methods are available than can attenuate those muscle mass changes. Exercise, nutrition, hormone replacement and vitamin D consumption are considered as important contributors to muscle mass, strength and quality of life. For instance, resistance training and adequate protein intake can help reduce the risk of sarcopenia and the loss of muscle. Balance exercises should also be proposed to postmenopausal women because of the increased risk of falls and fractures after menopause. Furthermore, isoflavone supplementation could potentially be effective to help elevate hormone concentration and act on muscle mass in postmenopausal women. This strategy, however, needs to be further studied (Figure 1).

In conclusion, studying the effects of menopause on muscle mass and function is important because of the increasing number of postmenopausal women in developed countries and the detrimental effects of the loss of muscle mass and strength. As such, finding strategies to counteract sarcopenia and muscle weakness in postmenopausal women has significant chances to reduce the financial and human burden associated with physical capacity impairment.

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