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Review

Menopause and sarcopenia: A potential role for sex hormones

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ABSTRACT

Menopause is associated with a decline in estrogen levels, which could lead to an increase in visceral adiposity as well as a decrease in bone density, muscle mass and muscle strength. This decline in muscle mass, known as sarcopenia, is frequently observed in postmenopausal women. Potential causes of sarcopenia include age-related changes in the hormonal status, low levels of physical activity, reduced protein intake and increased oxidative stress. However, the role of sex hormones, specifically estrogens, on the onset of sarcopenia is controversial. Preventing sarcopenia and preserving muscle strength are highly relevant in order to prevent functional impairment and physical disability. To date, resistance training has been shown to be effective in attenuating age-related muscle loss and strength. However, results on the effect of hormonal supplementation to treat or prevent sarcopenia are contradictory. Further research is needed to identify other potential mechanisms of sarcopenia as well as effective interventions for the prevention and treatment of sarcopenia. Therefore, the purpose of this review will be to examine the role of sex hormonal status in the development of sarcopenia. We will also overview the physical as well as metabolic consequences of sarcopenia and the efficiency of different interventions for the prevention and treatment of sarcopenia.

Contents

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1. Introduction

It is well known that menopause is characterized by important changes in hormonal status and that these changes have an important effect on bone mass density and body fat distribution [1]. In addition, a good body of evidence supports the hypothesis that the decline in estrogen levels with menopause may play a role in muscle mass loss in postmenopausal women [2]. The term that is widely used to describe the normal age-related loss in muscle mass is sarcopenia. Functional impairment and physical disability are the major consequences of sarcopenia and are associated with increased healthcare expenditures [3]. Indeed, it is estimated that the consequences of sarcopenia are responsible for approximately $18 billion in direct healthcare costs in the US annually [4]. Considering that the number of older adults is expected to double over the next 25 years, sarcopenia has become an important clinical research topic. Therefore, investigating the mechanisms underlying this condition and developing efficient interventions for the prevention and treatment of sarcopenia may be of great interest for health care professionals. In this review, we will (1) summarize the hormonal changes associated with menopause; (2) examine the role of sex hormones with regards to sarcopenia; (3) discuss the physical and metabolic consequences of sarcopenia and (4) address the potential effect of hormone replacement therapy and phytoestrogens supplementation combined or not with exercise training on muscle mass.

2. Menopause

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity and marks the end of natural female reproductive life. Menopause is preceded by a period of menstrual cycle irregularity, known as the menopause transition or peri-menopause, which usually begins in the mid-40s. The menopause transition is characterized by many hormonal changes predominantly caused by a marked decline in the ovarian follicle numbers [5]. A significant decrease in inhibin B appears to be the first endocrine marker of the menopause transition with follicle-stimulating hormone (FSH) levels being slightly raised [5]. Marked decreases in estrogen and inhibin A with significant increases in FSH are only observed in the late stage of menopause transition [5]. At the time of menopause, FSH levels have been shown to increase to 50% of final post-menopausal concentrations while estrogens levels have decreased to approximately 50% of the premenopausal concentrations [5]. Since the decrease in estrogen levels occurs in the fifth decade of life, this means that most women will spend more than 30 years in postmenopausal status.

A good body of evidence suggests that changes in hormonal status, particularly the decline in estrogen, in the menopause years may have a detrimental effect on women's health. Accordingly, it has been reported that the decrease in estrogen contributes to the decrease in bone mass density, the redistribution of subcutaneous fat to the visceral area, the increased risk of cardiovascular disease and the decrease in quality of life [1]. In addition, hormonal changes may also have a direct effect on muscle mass. That is, an accelerated decline in muscle mass has been shown to occur after the 5th decade, thus around the years of menopause [6]. Moreover, a cross-sectional study reported a decline in muscle mass of 0.6% per year after menopause [7]. Furthermore, changes in characteristics of muscle tissue during menopause have been reported. Accordingly, Jubrias et al. [8] showed that postmenopausal women had twice the amount of non-contractile muscle tissue, such as intramuscular fat, compared to younger women.

3. Definition of sarcopenia

Sarcopenia refers to the loss of muscle mass associated with normal aging [8]. However, over the past decade, sarcopenia has often been defined as the age-related loss in muscle mass and muscle strength, which implies that these are causally linked and that changes in muscle mass are directly and fully responsible for changes in muscle strength. However, this concept has been challenged since it has been shown that age-associated changes in muscle mass explained less than 5% of the variance in muscle strength [9]. Thus, in this review, the term sarcopenia will be used only to refer to the age-related loss in muscle mass.

Although there has been an increasing interest to investigate the functional consequences and biologic mechanisms of sarcopenia, no international definition has been proposed to identify sarcopenic individuals. Most of the studies investigating sarcopenia have used a muscle mass index by dividing total muscle mass or appendicular muscle mass, measured by dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA), by height squared [10–14]. According to these definitions, class I sarcopenia is defined as a muscle mass index of 1–2 standard deviations below the values of a younger reference population [10,12,13] whereas class II sarcopenia represents a muscle mass index of 2 standard deviations or more below the values of the same younger reference population [10–14].

4. Changes in muscle morphology with sarcopenia

All skeletal muscles are composed of motor units and each motor unit contains a motor neuron and muscle fibers. Motor units can be differentiated in two main types based on the fiber type present in the motor unit. Slow motor units are mainly composed of type I fibers while fast motor units predominantly consist of type II fibers [15]. The decrease in muscle mass with aging results from loss of both slow and fast motor units, with an accelerated loss of fast motor units [16]. Moreover, there appears to be an atrophy of type II fibers [16]. As motor units are lost via denervation, surviving motor units recruit denervated fibers, changing their fiber type to that of the motor unit [15]. Thus, there is a net conversion of type II fibers to type I fibers, as type II fibers are recruited into slow motor units [15]. Clinically, the loss of fast motor units and consequently of type II fibers results in loss of muscle strength and power which is necessary for physical movements such as rising from a chair, climbing steps or regaining posture after a perturbation of balance [15]. Another morphologic aspect of the aging skeletal muscle is the infiltration of the muscle tissue by lipids whether by an increase in the adipocyte number [17–19] or an increased deposition of lipid in muscle fibers [20–22].

5. Epidemiology of sarcopenia

The prevalence of sarcopenia highly depends on the criteria used to identify sarcopenic individuals. To our knowledge, only one study investigated the prevalence of sarcopenia in a representative sample of men and women aged 18–80 years old [12]. Indeed, Janssen al. [12] observed that the prevalence of class I and class II sarcopenia increased from the third to sixth decade and remained relatively constant thereafter. In addition, it was reported that the prevalence of class I and class II sarcopenia was 50% and 7%, respectively in women aged between 50 and 59 years old (Fig. 1). This is a 15% increment in the prevalence of class I sarcopenia compared to women aged 40 to 49 years suggesting that the prevalence of sarcopenia increases at the time when significant changes in the hormonal status occur.

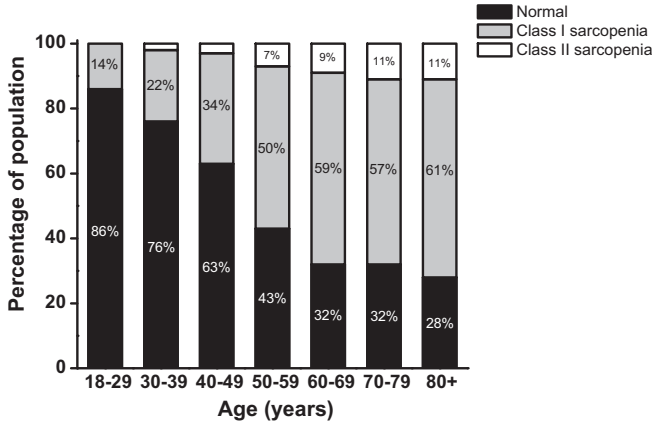

Fig. 1. Prevalence of sarcopenia in women aged 18–80 years old. Adapted from Janssen et al. [12].

6. Role of menopause associated with hormonal changes

It has been hypothesized that menopause transition and the subsequent decline in estrogen may play a role in muscle mass loss [23–26]. That is, van Geel et al. [27] reported a positive relationship between lean body mass and estrogen levels. Similarly, Iannuzzi-Sucich et al. [28] observed that muscle mass is correlated significantly with plasma estrone and estradiol levels in women. However, Baumgartner et al. [29] reported that estrogen levels were not associated with muscle mass in women aged 65 years and older. The mechanisms by which a decrease in estrogen levels may have a negative effect on muscle mass are not well understood but it has been suggested that the decrease in estrogen concentrations may be associated with an increase in pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) or interleukine-6 (IL-6), which might be implicated in the apparition of sarcopenia [30]. Furthermore, estrogen could have a direct effect on muscle mass since it has been shown that skeletal muscle has estrogen beta-receptors on the cell membrane, in the cytoplasm and on the nuclear membrane [31]. Therefore, a direct potential mechanistic link could exist between low estrogens levels and a decrease in protein synthesis. Further studies are needed to investigate this hypothesis. Nevertheless, before reaching a conclusion on the contribution of estrogens to the onset of sarcopenia, it would be important to measure urinary estrogen metabolites since a relationship between breast cancer and urinary estrogens metabolites has been shown [32].

With aging, free testosterone levels are decreased in men and this decline parallels the decrease in muscle mass and muscle strength [33]. Evidence to support testosterone supplementation in men is variable as some studies have observed an increase in muscle mass while others have not [34]. In women, bio-available testosterone levels are also decreased, particularly in the immediate years after menopause [35,36]. This observation raises the question whether the decline in testosterone levels plays a role in the accelerated loss in muscle mass with menopause. Further studies are needed to investigate the relationship between testosterone and muscle mass in women as well as testosterone supplementation in sarcopenic women.

Another hormone associated with muscle mass loss is dehydroepiandrosterone (DHEA), a pro-hormone that can transform into sex steroid such as androgens and estrogens. Among the numerous important roles of DHEA in the human body, 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 [37]. Circulating levels of DHEA decline with age, especially at menopause in women [2]. This decline in DHEA has been shown to be associated with a decrease in muscle mass and physical performance [37]. However, Abbasi et al. [38] did not observe a relationship between DHEA levels and body composition in women aged 60 years and older. Furthermore, in elderly individuals, DHEA replacement showed no improvement in physical performance and body composition [39]. Moreover, supplementation in DHEA (50–100 mg per day) for 3–9 months has shown no beneficial effect for improving muscle mass [35]. Additional randomized controlled trials are needed before reaching valid conclusions as to the clinical utility of DHEA supplementation in the management of sarcopenia.

Other factors contribute to the development of sarcopenia are shown in Fig. 2: (1) increased inflammatory activity as measured by IL-6 or TNF-α which contributes to muscle catabolism; (2) accumulation of free radicals with contributes to oxidative stress; (3) changes in mitochondrial function of muscle cells; (4) increased apoptotic activity affecting muscle function; (5) reduced physical activity; and (6) impaired nutrition. The contribution of these factors to the development of sarcopenia in women and men has been the subject of numerous reviews [2,15,40,41].

As mentioned above, menopause is associated with a rapid decline in muscle mass while sarcopenia refers to the loss of muscle mass with age. Since muscle mass is influenced by many factors that are all related to age and menopause status, it makes it thus difficult to establish the relative contribution of menopause as opposed to age on the onset of sarcopenia. However, the loss in muscle mass is gender-specific as the prevalence of sarcopenia in women increases around the age of 50 whereas in men the prevalence increases by the sixth decade. Thus, the role of menopause in the development of sarcopenia can be hypothesized but further studies are needed to specify its contribution.

7. Hormone replacement therapy (HRT) and phytoestrogens for improving muscle mass

Estrogen supplementation or HRT is considered as a potential strategy to play a protective role on muscle mass and muscle strength although contradictory results have been reported. For example, Sorensen et al. [42] performed a 12-week double-blind study where estrogen or placebo was administered and observed a significant increase in lean body mass. Moreover, in the Women's Health Initiative study, subjects who were randomized to receive HRT for 3 years lost 0.04 kg of lean body mass, which was significantly less than the 0.44 kg lost by women on placebo, indicating that HRT could reduce muscle mass loss [43]. However, some studies have failed to show a positive effect of HRT on muscle mass [44–46]. That is, in a study conducted by Hansen et al. [44], women were given 20 mg doses of estrogen for 64 weeks and the increase in muscle mass was not significant. In addition, the incidence of sarcopenia was investigated in women who had been on HRT for at least 2 years. It was reported that women on HRT had a 23% incidence of sarcopenia whereas those not on HRT had a 22% incidence suggesting that HRT does not prevent the development of sarcopenia [45]. Nevertheless, the contradictory results between studies could be explained by some confounding factors such as the dose of estrogen used, the duration of the study, levels of physical activity, diet and medications [31]. It is also possible that the differences seen are due to different times of post-menopause when HRT is being used, with the more beneficial effects of HRT being in the early post-menopause period [36].

Resistance training has been shown to be effective in attenuating age-related muscle loss [47]. To our knowledge, at least two studies combined resistance training with HRT [48,49]. Sipila et al. [48] randomized 80 postmenopausal women to four differ-

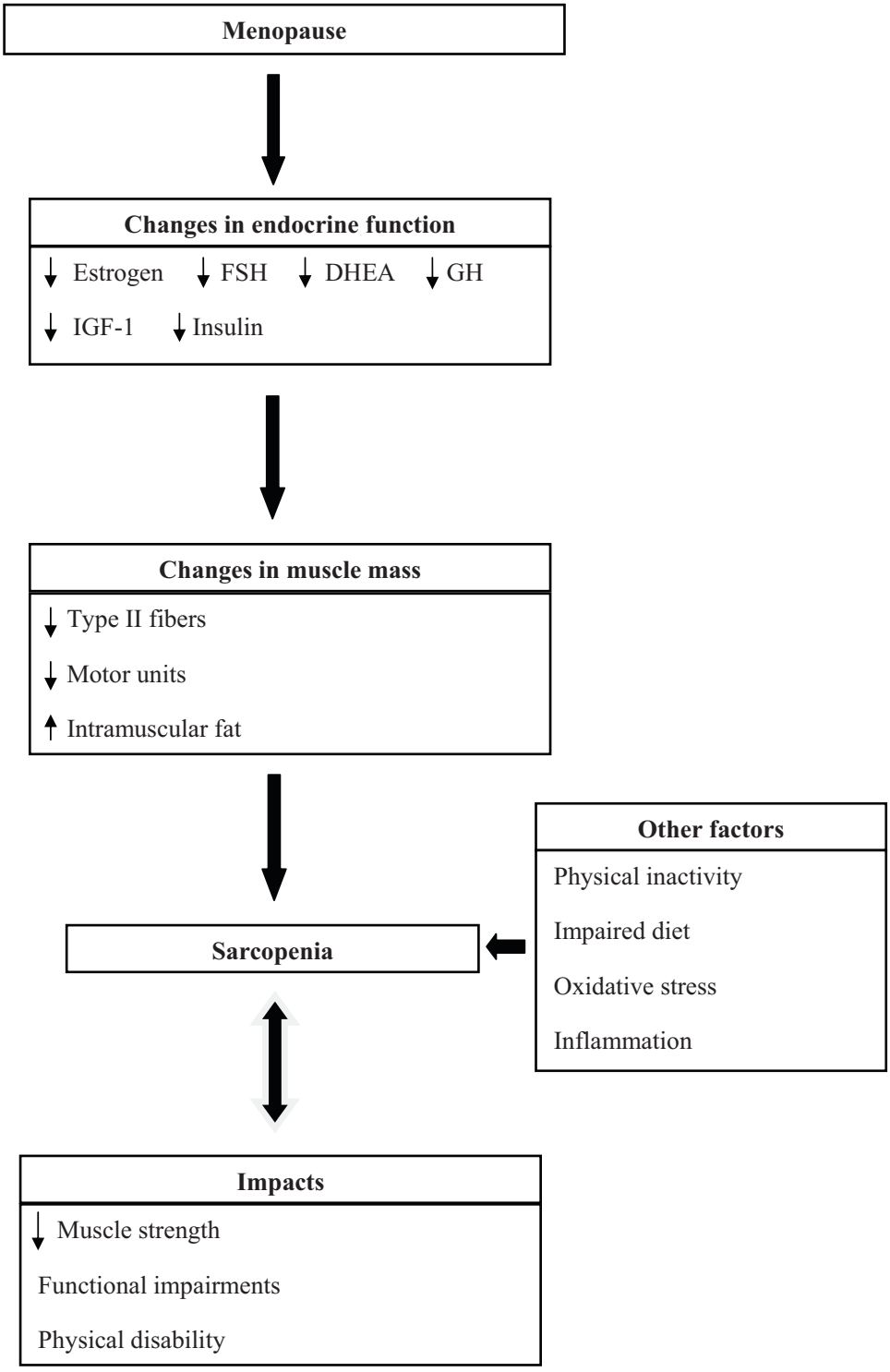

Fig. 2. Menopause-related changes on muscle mass and its impact on functional status.

ent groups: (1) resistance training only (2 supervised sessions per week for 12 months); (2) HRT only for 12 months; (3) resistance training combined with HRT or; (4) control group. Women performing resistance training combined with HRT or receiving HRT alone significantly increased quadriceps cross-sectional area (+7.1% and +6.3%, respectively) compared to the exercise only (+2.2%) or the control (+0.7%) group. Furthermore, in a partially randomized design, Teixeira et al. [49] assigned women who were already users or non-users of HRT to exercise or non-exercise groups. The resistance exercise training program consisted of 3 training sessions per week for 12 months. Increases in lean body mass were observed in the HRT + exercise (+1.0 kg) and HRT only (+0.3 kg) groups. The results of these studies suggest that HRT by itself may preserve muscle mass. Thus, the combination of HRT and resistance training may not be more beneficial than HRT alone for the prevention of sarcopenia in postmenopausal women. However, given the possible increased risk of cardiovascular disease and breast cancer associated with the use of HRT [50], estrogen supplementation

should not be recommended as a primary line of treatment for sarcopenia.

Another prospective approach to counteract sarcopenia might be phytoestrogen supplementation. Isoflavones supplements are found in soy products and exert a lipid-lowering effect [51], favor vasodilatation as well as arterial compliance [52] and contribute to the regulation of fasting glucose and insulin levels [53]. In addition, Aubertin-Leheudre et al. [54] investigated the effect of a 70 mg/day of soy isoflavone supplementation for 24 weeks on muscle mass in obese-sarcopenic postmenopausal women and observed that isoflavone supplementation was associated with a significant increase in appendicular fat-free mass (+0.5 kg), but this increase was not enough to reverse sarcopenia. Moreover, Moeller et al. [55] randomized postmenopausal women to receive either isoflavone-rich soy protein (40 g), isoflavone-poor soy protein or when protein (control) for 24 weeks. It was reported that changes in total lean body mass were not different between groups; however, lean body mass at the hip increased to a greater extent in the isoflavone-rich group (+3.4%) than in the isoflavone-poor (+1%) or control (0%) groups. Finally, Maesta et al. [56] assessed the effect of soy protein (25 g) combined with resistance training on body composition in postmenopausal women. This study showed that soy protein combined with 16 weeks of resistance training 3 times per week did not result in greater increases in muscle mass compared to resistance training alone suggesting that soy protein had no influence on muscle mass.

8. Consequences of sarcopenia

Several studies have shown an association between the loss in muscle mass and adverse clinical outcomes such as mobility limitations and fractures. That is, Janssen et al. [12] used the data of the Third National Health and Nutrition Examination Survey to investigate if sarcopenia was related to functional impairment and physical disability. Functional impairment was defined as having limitations in mobility performance such as walking and climbing stairs while physical disability refers to difficulty of performing activities of daily living (shopping, light household chores). This study showed that the prevalence of functional impairment and physical disability was greater in class I and class II sarcopenia individuals than in their counterparts without sarcopenia [12]. The results of Janssen et al. [12] are consistent with those of Baumgartner et al. [57] who reported that sarcopenia was a associated with disability, the use of a cane or walker and a history of falling in a sample of 808 men and women. In addition, it was shown that lower extremity performance score, assessed using chair stands, gait speed and standing balance, was lower in sarcopenic women compared to nonsarcopenic women [58]. Furthermore, longitudinal studies have been undertaken to determine if sarcopenia precedes the onset of functional impairments and physical disability. Indeed, Visser et al. [59] reported that low muscle mass resulted in a 34% increased risk of mobility limitations 5 years later in women. The same study also showed that women in the lowest quartile of muscle mass had a 30 to 40% increased risk for the inability to perform activities of daily living [59]. Recently, Woo et al. [14] showed that sarcopenic individuals presented greater limitations in climbing stairs and in general activities of daily living after 4-years of follow-up.

Little is known about the association between sarcopenia, metabolic risk factors and health status. In the cross-sectional analysis of the New Mexico Aging Process Study, obese sarcopenic individuals did not show a higher prevalence of congestive heart disease [11]. Interestingly, the prevalence of the metabolic syndrome was higher in obese nonsarcopenic subjects (37.5%) than in obese sarcopenic individuals (19.2%) [11]. Furthermore, Aubertin-Leheudre et al. [10] reported that nonsarcopenic obese postmenopausal women presented more cardiovascular risk factors (higher triglycerides, lower HDL-cholesterol) compared to obese sarcopenic postmenopausal women. Similarly, Messier et al. [13] observed that insulin resistance and fasting glucose tended to be lower in obese sarcopenic women compared to obese nonsarcopenic women. As mentioned earlier, because type II muscle fibers are recognized to be glycolytic and insulin-resistant, the accelerated loss of type II fibers with aging may explain how sarcopenia would positively alter glucose metabolism [10]. Nevertheless, it should be noted that the physical and metabolic consequences of sarcopenia discussed here are neither specific to menopause nor gender-specific.

9. Conclusion

The decrease in estrogens levels with menopause may play a potential role in the decline in muscle mass after the 5th decade of life. Sarcopenia is a complex condition involving hormonal, biological, nutritional and physical activity mechanisms. It is however difficult to establish the relative contribution of sex hormones on the onset of sarcopenia. Prospective observational studies with regular measurement of sex hormones and body composition during menopause transition, taking into account confounding factors such as nutrition and physical activity, will have to be undertaken in order to determine the contribution of menopause in the development of sarcopenia. Furthermore, the measurement of urinary estrogens metabolites could add new evidence as for the role of estrogens in sarcopenia. It remains certain, though, that the decline in muscle mass is associated with an increased risk of functional impairment and physical disability. Finally, further randomized controlled trials are needed to investigate the effects of physical activity as well as hormone and phytoestrogen supplementation on sarcopenia.

Competing interests

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Contributors

Virginie Messier: drafting; Rémi Rabasa-Lhoret: revision; Sébastien Barbat-Artigas: revision; Belinda Elisha: revision; Antony D. Karelis: revision; Mylène Aubertin-Leheudre: revision.

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