Research paper

Muscle strength and bone in healthy women: effect of age and gonadal status

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ABSTRACT

OBJECTIVE: The aim of this work was to examine the effects of age and menopause on muscle strength and on the muscle-bone interaction. DESIGN: One hundred ninety-four healthy women (mean age 49.8 ± 12.6 SD years) were assessed. Maximal Voluntary Contraction (MVC, Newton, N) by Hand Grip Dynamometer, bone mineral density at one third of the radius (R-BMD) by dual-energy X-ray absorptiometry (DXA) and phalangeal ultrasound by the DBM Sonic 1200 device were evaluated at the upper dominant limb. Ultrasonometric parameters considered were Amplitude-Dependent Speed of Sound (ADSoS) and Ultrasound Bone Profile Index (UBPI). RESULTS: MVC significantly decreased with age (r^2=-0.12, p<0.005). For each level of age, fertile women had a greater MVC compared to postmenopausal women (r^2=0.015, p<0.005). In the whole sample, a statistically significant correlation between MVC and R-BMD (r=0.354, p<0.001) and between MVC and ADSoS (r=0.294) and UBPI (r=0.311)(p<0.001 for both) were observed. CONCLUSIONS: We conclude that age and menopausal status significantly contributed to the reduction of muscle strength. The decline of muscular strength significantly correlated with quantitative and qualitative bone features.

Key words: Age, Bone, Menopause, Muscle, Strength

INTRODUCTION

Muscle strength plays a widely recognized key role in overall functional status, particularly in the elderly.[1,2] Skeletal muscle impairment is closely associated with a decline of daily activities, increased risk of institutionalization, cognitive decline and accelerated mortality.[1-3] Several important factors may affect muscle strength, including age, BMI, gonadal status, level of physical activity and nutritional factors.[4-6] Age-related muscle loss occurs at an earlier

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time in women compared to men because of ensuing changes in hormonal status in menopause.[7,8] In fact, however, though the age-related decline of muscle strength has been partly associated with the decreased estrogen levels of postmenopausal women,[8] the effect of menopause and aging have not been clearly described in previous studies.[8,9]

To simply and accurately measure muscle strength, isometric strength has frequently been assessed, since it correlates with the force-producing capabilities of muscles.[10] In particular, it has been demonstrated that handgrip strength is positively related to lower and upper muscular strength so that it is considered a surrogate measure of overall muscular strength.[1,11,12] Accordingly, an increase in handgrip strength has been linked to an increased lean body mass; moreover, handgrip strength is considered a predictor of all-cause mortality among elderly people.[1]

Muscle mass and strength also exert an important impact on bone strength.[13] The relationship between bone mineral density (BMD), lean mass and muscle strength has been widely described, and age-related bone loss has been associated with a decrease in muscle mass and function.[14,15] Furthermore, several studies showed that muscle load exerts a positive influence on bone independent of body weight, which accounts for the well-known beneficial effect of physical activity on skeletal tissue.[13-16] Some authors also suggested a regional effect of muscular strength on BMD. Blain et al. reported a site-specific effect of muscular strength of quadriceps on bone remodeling at the femoral neck in a group of healthy postmenopausal women,[17] and Di Monaco et al. found a positive correlation between distal radius BMD and handgrip strength among postmenopausal women.[18] Moreover, a correlation between handgrip strength, BMD and fractures has frequently been reported.[14,15,19] However, to our knowledge, there are no data focusing on the relationship between muscle strength and skeletal tissue, both evaluated at specific sites in pre- and postmenopausal women.

The aim of this study was to evaluate changes of muscle strength of the upper dominant limb with respect to age and gonadal status in a large sample of healthy women. Muscle strength assessed via BMD at forearm and by phalangeal quantitative ultrasound, was also studied in order to assess the possible influence of muscle function on quantitative and qualitative parameters of skeletal tissue.

SUBJECTS AND METHODOLOGY

One hundred ninety-four healthy volunteers from the female personnel of our Hospital were studied. None of the women took drugs which interfere with bone metabolism, or was on hormone replacement therapy, or was engaged in resistance training activities, or was a current smoker. Postmenopausal status was defined as the absence of menses for more than 12 months.

We evaluated isometric grip strength of the upper dominant limb using a hand held dynamometer in all subjects (Hand Grip Dynamometer). This instrument is part of the experimental Facility "Hand Posture Analyzer", a payload composed by a set of instruments designed and developed by Kayser Italia s.r.l. under ASI (Italian Space Agency) contract. The fact that the test is easy to perform and is completed in about five minutes allows us to routinely use the instrument in clinical practice in every age group. The "Hand Posture Analyzer" Facility consists of Hand Grip Dynamometer and Pinch Force Dynamometer tools, which are isometric dynamometers designed and manufactured respectively for best handgrip and pinch force application. Hand Grip Dynamometer and Pinch Force Dynamometer force ranges are respectively 40 – 1000 Newton and 0 – 270 Newton with a measurement accuracy of 0.75% of the full scale. Maximal voluntary contraction (MVC, Newton, N) force was measured in the sitting position in each subject. The short-term imprecision for MVC was calculated on 14 normal subjects measured 5 times each and was $<5\%$.

BMD was measured by dual-energy X-ray absorptiometry (Hologic QDR 4500A, Hologic Inc., USA) at one third of the radius of the upper dominant limb (R). Quantitative ultrasound of the proximal phalanges was assessed using the DBM Sonic 1200 device (IGEA, Carpi, Italy) at the distal metaphysis of the last four fingers of the dominant hand. Ultrasonometric parameters considered were speed of propagation of ultrasound dependent on the amplitude of the ultrasound wave crossing bone tissue

(Amplitude-Dependent Speed of Sound, ADSoS) and a parameter calculated by computer analysis of dynamic parameters of ultrasound signal (Ultrasound Bone Profile Index, UBPI). The short-term precision of ultrasonometric parameters was calculated on ten normal subjects measured five times each. The CVs for the single parameters were 0.63% for ADSoS and 2.1% for UBPI.[20]

Statistical analysis

Results are presented as mean values ± SD. The sample was subdivided according to gonadal status and, after normality testing, comparison between MVC in premenopausal and in postmenopausal women was performed by unpaired t-test. We used a linear and quadratic regression models and broken-line regression models to determinate the relative effect of age and menopause on muscle strength. In particular, the broken-line regression models may explain different linear relationships between the response variables and the covariates before and after unknown change points. All statistical analyses were performed in statistical software R (www.r-project.org). To investigate correlations between MVC, densitometric and ultrasonometric parameters we used the Spearman correlation coefficient. Significance was set at p value <0.05.

RESULTS

Table 1 depicts the mean values±SD of demographic characteristics and of the parameters studied. Out of 194 women, 92 were pre- and 102 postmenopausal; mean age±SD, 49.8 ± 12.6 years, range 21-82 yrs; BMI 24.1 ± 3.8 kg/m^2. As shown, mean values of R-BMD, ADSoS, UBPI and MVC were significantly higher in premenopausal than in postmenopausal women ($p<0.001$ for all).

Figure 1A, depicts the relationship obtained by fitting a quadratic regression model between MVC and age and adjusting for the menopause variable. The estimated equation is: $MVC = 116.69 + 4.89 \times age - 0.05 \times age^2 - 26.64 \times menopause$. This model indicates that, for each level of age, fertile women had a greater MVC value than postmenopausal women. The r^2 index was 0.015 and all the terms are significant ($p<0.005$ for linear term; $p<0.005$ for quadratic term; $p<0.05$ for menopause). This model fitted the data significantly better than the previous one ($p<0.05$).

Figure 1B depicts the relationship obtained by fitting a broken-line regression model between MVC and age. The model shows a statistically significant increase in MVC values up to the age of 40.08 (s.e. 3.9 yrs), which represents the estimated split point. With this model MVC increased at the rate of 2.388 N for years before the split point ($p=0.1$) and it decreased at the faster rate of 4.72 N for year after the split point ($p<0.01$). The r^2 value was 0.14.

Table 2 depicts the statistically significant correlations between MVC and R-BMD ($r=0.354$, $p<0.001$) and MVC and ultrasonometric parameters (ADSoS $r = 0.294$; UBPI $r = 0.311$, $p<0.001$ for both) in the

Table 1. Mean values ± SD of demographic characteristic and of all parameters in the whole sample and in the sample subdivided according to gonadal status

Parameters	Whole sample (n=194)	Premenopausal (n=92)	Postmenopausal (n=102)	p[a]
Age (yrs) *Menopausal duration*	49.8 ± 12.6	40.2 ± 9.2	58.5 ± 8.2 *(10.8 ± 10.4)*	<0.001
Height (cm)	159.9±6.8	161.3±5.7	158.6±7.49.9	<0.01
Weight (kg)	61.6±10	61±10.1	62.2±9.9	NS
BMI[b] (kg/m^2)	24.1 ± 3.8	23.4 ± 3.9	24.7 ± 3.6	<0.01
MVC[c] (N)	205 ± 53.5	222 ± 49.3	190 ± 52.6	<0.001
R-BMD[d] (g/cm^2)	0.663±61.9	0.690 ± 43.6	0.639 ± 65.9	<0.001
ADSoS[e] (m/s)	2066 ±92.1	2127 ± 60.6	2011 ± 80.2	<0.001
UBPI[f]	0.620±0.189	0.733 ± 0.130	0.518 ± 0.176	<0.001

[a]Unpaired t-test between premenopausal and postmenopausal women, [b]Body mass index, [c]Maximal voluntary contraction, [d]Bone mineral density at one third of the radius, [e]Amplitude-dependent speed of sound, [f]Ultrasound bone profile index.

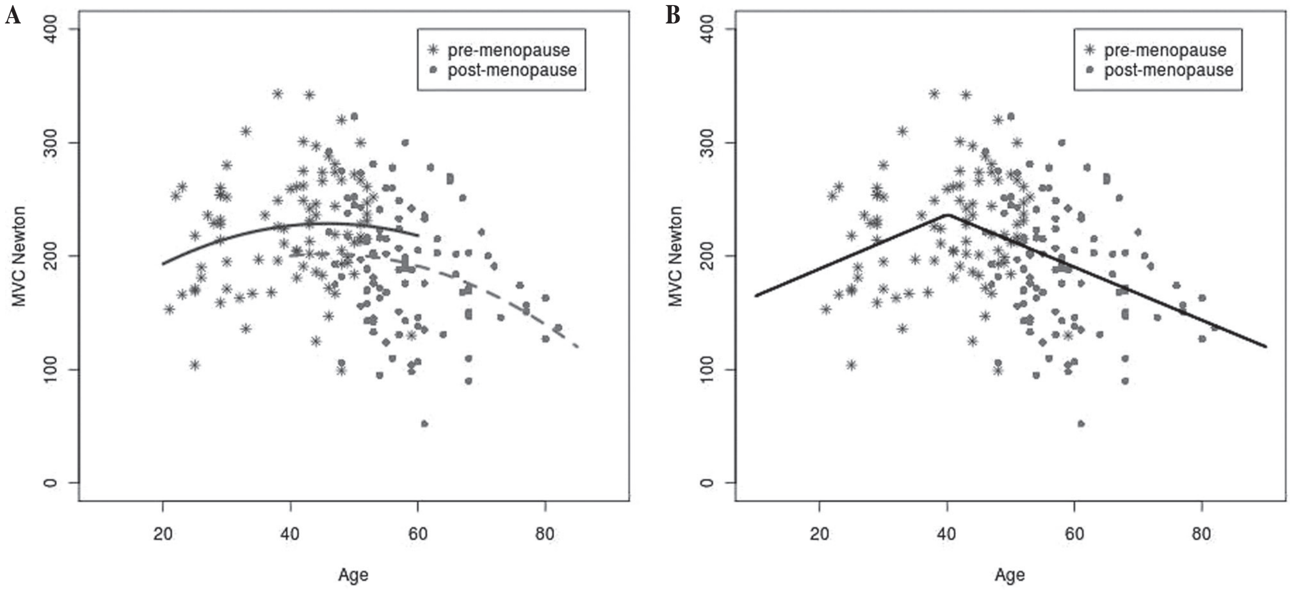

Figure 1. A: Relationship between MVC and age in the whole sample (n=194) by adding the menopause variable. The estimated equation is MVC = 116.69 + 4.89 x age – 0.05 x age^2 – 26.64 x menopause. **B:** Estimated split point in the correlation between MVC and age in the whole sample (n=194). MVC values significantly increases up to the age of 40.08 (s.e. 3.9 yrs), which represents the estimated split point.

whole sample. These correlations were significant only in postmenopausal women group (MVC vs R-BMD r = 0.354 p<0.001; vs ADSoS r = 0.307; vs UBPI r = 0.319, p<0.01 for all). By contrast, handgrip strength values did not correlate with both densitometric and ultrasonometric parameters in the premenopausal group. As far as BMI is concerned, we found no significant correlation with MVC values, both in the whole sample and in the groups of pre- and postmenopausal women, separately considered (data not shown).

Table 2. Correlation matrix between MVC, densitometric and ultrasonometric parameters in the whole sample and in the sample subdivided according to gonadal status

		Whole sample (n=194)	Premenopausal (n=92)	Postmenopausal (n=102)
Parameters		**MVC[a] (N)**	**MVC (N)**	**MVC (N)**
R-BMD[b] (g/cm²)	r	0.354	0.111	0.354
	p[c]	0.0001	0.290	0.0001
ADSoS[d] (m/s)	r	0.294	-0.187	0.307
	p	0.0001	0.07	0.01
UBPI[e]	r	0.311	-0.033	0.319
	p	0.0001	0.753	0.01

[a]Maximal voluntary contraction, [b]Bone mineral density at one third of the radius, [c]Spearman correlation coefficient, [d]Amplitude-dependent speed of sound, [e]Ultrasound bone profile index.

DISCUSSION

In this work we have investigated the relative influence of age and hormonal status on muscle strength of the upper dominant limb in a large sample of healthy women, as well as the correlation between muscle strength and quantitative and qualitative features of skeletal tissue. We have found that handgrip strength was strongly associated with age, with a trend that showed a significant increase of muscle strength up to the age of 40 years. Subsequently, muscle strength progressively and significantly decreased (Figures 1). Our results are in line with those of Lauretani et al who found a significant relationship between age and handgrip strength and suggested that isometric muscle strength and muscle power considerably decline with age.[21] Previous studies reported a peak of muscle mass between the second and the fourth decade of life, with a subsequent steady decrease with aging of approximately 1% per year.[9,21,22] Indeed, we observed a rapid decline of muscle strength after the age of 40 at the rate of 4.72 N per year (Figure 2).

The decline of muscle strength with age can be ascribed to the well-known decrease in muscle mass and quality, commonly defined as age-related sarcopenia.[12] Sarcopenia is a common feature among elderly people, the prevalence of which ranges from 13% to 24% in persons aged over 60 years to more than 50% in those 80 yrs and older.[24] Sarcopenia is also associated with several adverse outcomes, such as many chronic disorders, physical disability, poor quality of life and increased mortality.[12,25] Several mechanisms contribute to age-related sarcopenia, such as decreased physical activity and nutritional intake, oxidative stress, inflammatory insults and hormonal changes.[26] Among other factors, sex steroids are of huge importance for skeletal muscle health. Several studies reported a fast rate of loss in muscle mass and strength during perimenopausal years,[23] the age-related changes in gonadal status significantly influencing the development and progression of sarcopenia and functional decline in the elderly.[12] In this context, our data demonstrate that the mean level of MVC in premenopausal women was significantly higher than in postmenopausal women and that, at every age, postmenopausal women had a MVC value lower than the fertile ones (Figure 2). However, data on this matter are still conflicting and the effect of menopause on muscle strength has not been well established.[8] Some authors reported that the relative contribution of menopause as compared to that of age on muscle loss remains undefined. In fact, many factors influencing muscle mass, such as low physical activity, inflammatory factors, leg strength and power, low protein and vitamin D intake and BMI could be negatively affected by both age and menopausal status.[8] On the other hand, other findings suggested a direct effect of sex steroids on skeletal muscle, supporting the hypothesis of a specific correlation between muscle tissue characteristics and estrogen metabolism, as well as between muscle strength and circulating estrogen levels.[8] Estrogen receptors (ERs) are actually present in muscle membranes, cytoplasm and nuclei and a greater number of ERs in muscle fibers was demonstrated in children and in adult men and women as compared to postmenopausal women.[27] Our results, in agreement with these latter findings, showed that menopause could be considered as a crucial factor directly influencing muscle strength, regardless of age.

We have found that muscle strength was strongly associated with several quantitative and qualitative parameters of bone condition. As shown in Table 2, radial BMD and all ultrasonometric indices were significantly associated with MVC in all subjects ($p<0.001$) and also in postmenopausal women ($p<0.001$ and $p<0.01$, respectively). These findings are in line with previous studies reporting a positive correlation between BMD and muscle strength at both upper and lower limbs. A significant positive correlation between distal radius BMD and handgrip strength, the latter being the strongest independent predictor of radial BMD, was shown by Di Monaco et al. in postmenopausal women.[18] Frank et al. reported that isometric, concentric and eccentric handgrip torques significantly contribute to the prediction of bone strength, evaluated by radial peripheral quantitative computed tomography, in postmenopausal women with forearm BMD T-score above the osteoporotic threshold.[28] Blain et al. reported a significant influence of quadriceps strength on femoral neck BMD, but not on lumbar spine BMD variance, in a group of healthy women aged more than 60 years, suggesting the hypothesis of a regional effect of muscle forces on BMD.[17] Our results further support the hypothesis of a site-specific effect of muscle strength: forces arising from muscular loading and contraction not only influenced BMD but also bone quality and microarchitecture, at least in postmenopausal women.[14,17,29-32] Quantitative ultrasound is a validated technique in acquiring information about qualitative and structural features of bone and in identifying individuals at risk for fractures.[20] To our knowledge, this is the first study evaluating the relationship between handgrip strength and qualitative features of bone, both assessed at the upper dominant limb. In adjunct, whilst previous studies chiefly focused on postmenopausal women, we investigated a large sample of both pre- and postmenopausal women. This is a major strength of our research, since it allowed us to effectively compare the effects of both age and menopausal status on muscle strength and the relationship between muscle strength and bone in women.

Hence, the influence of muscle strength on skeletal health seems to depend on gonadal status, since handgrip strength was significantly associated with BMD and ultrasonometric parameters in the whole sample, but not in premenopausal women. Our findings did not show any significant correlations between bone mass and quality on the one hand and muscle strength on the other in hormonally replete adults; on the contrary, the effect of muscle force on bone turned out to be significant only when the anabolic effects of estrogens on the skeleton was missing.

Our observation could partly be explained in the light of the previously reported low correlation between muscle strength and BMD in young and active individuals.[33] Even in athletes, once the peak bone mass is reached, the further increase in muscle strength does not result in a further rise in bone mass.[33] A possible influence of other factors, such as vitamin D status, can also be hypothesized. In this regard, the absence of data about estrogen and vitamin D serum levels also represents a limitation of our study.

The results we obtained have relevant clinical implications, since the loss of muscle strength with aging is associated with an increase in body sway, a greater risk of falls and fractures, increased disability and decreased survival rates following critical illness.[24] Moreover, isometric handgrip strength has been correlated with bone mass and the risk of fracture, as well as with the functional decline, grade of disability and mortality risk in the elderly.[1,12,14,15,19,21] We would therefore suggest that a clinical evaluation of muscle strength could be a useful additional tool in the overall evaluation of functional status and could valuably integrate any algorithm aimed to evaluate fracture risk in postmenopausal women. An important limitation is the fact that the cross-sectional design of our study does not allow us to draw firm conclusions on long-term change in muscle strength and its correlation with changes of bone mineral density and quality. Nevertheless, our results also suggest that physical training should be strongly recommended to ameliorate muscle strength and balance, to reduce fracture risk and to improve the overall functional status in postmenopausal women.[15,18,34,35] Though the optimal type and regimen of physical exercise is still debated, a recent meta-analysis reported that in postmenopausal women non weight-bearing progressive resistance strength exercises for lower limbs and a combination of exercise programmes are the most effective physical interventions on BMD of femoral neck and lumbar spine, respectively.[36] A significant decrease in bone loss and improvement in postural control was also reported in postmenopausal osteopenic women participating in Tai Chi training.[37,38] Moreover, gender differences in the muscle-bone unit and in the age-related bone loss suggest that different training strategies may be needed in women and in men.[39] For instance, in men aged 50-79 years lumbar spine and femoral neck BMD and strength improved after 18 months of progressive resistance training exercises with alternate days of weight-bearing activities.[40] Despite these results, there is as yet no definition as to which are the most efficient types of exercise specifically improving bone mass and strength in subjects of different age and sex.[41]

In conclusion, our results show that age and menopause significantly contribute to the reduction of isometric contraction of skeletal muscles. The degree of muscle strength of the dominant arm significantly correlates with some quantitative and qualitative features of skeletal tissue at this level. This finding underlines the relevance of extra-skeletal factors in influencing bone health.

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