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Original Article

Favorable effects of skeletal muscle on bone are distinguished according to gender and skeletal sites

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Abstract

Objectives: The aim of this study was to investigate associations between skeletal muscle mass and bone mineral density according to gender and skeletal sites.

Methods: Using the data from Korean National Health and Nutrition Examination Survey (KNHANES IV) 2009, a total of 711 males and 847 females over 65 years of age were evaluated. Bone mineral density (BMD) and body composition were assessed using dual-energy X-ray absorptiometry.

Results: Relative appendicular skeletal muscle (RASM) was positively related with the femur BMD with a stronger relationship in males ($r = 0.207$, $p < 0.001$) than in females ($r = 0.095$, $p < 0.05$). However, lumbar spine BMDs in both males and females did not show any significant associations with the RASM value. In the logistic regression for osteoporosis expressed as a decrease of risk per increase of RASM by 1 standard deviation (SD) of the same sex healthy reference group, the age- and BMI-adjusted odds ratio (OR) for osteoporosis was 0.42 (95% CI 0.12–0.76) in the femur neck and 0.24 (95% CI 0.07–0.76) in the total hip for males. Among females, the age- and BMI-adjusted OR for osteoporosis was 0.65 (95% CI 0.33–1.00), which showed importance only in the total hip.

Conclusions: Higher RASM was significantly associated with lower risk for osteoporosis and the areas at the femur neck and total hip appeared to more likely be affected positively by muscle. Moreover, because males showed faster muscle loss with aging than females, the bones of males may be more prone to favorable effects of muscle.

Keywords: Aging; Sarcopenia; Osteoporosis; Body composition

1. Introduction

Loss of muscle mass is a universal consequence of aging [1]. Sarcopenia is a condition characterized by progressive loss of muscle mass and strength and decreased physical performance [2]. Because of the considerable roles of skeletal muscle in humans, sarcopenia appears to result in many metabolic and physiological derangements in some individuals [3–5]. Therefore, many clinical and basic studies have recently been conducted regarding the clinical impact, pathophysiology, and treatment of sarcopenia [6]. Skeletal muscles are essential for locomotion and mobility, thus sarcopenia has dramatic consequences such as impaired performance, increased risk of falls and, consequently, an increased risk of fragility fractures [7–9].

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Osteoporosis, characterized by decreased bone strength and increased risk of fractures, is another major health problem faced by the elderly, and bone mineral density (BMD) and bone quality are major component determining bone strength [10]. Muscle and bone are well known to closely interact with each other [11,12]. Several theories have been suggested to explain the close relationship between sarcopenia and osteoporosis. First is the mechanostat theory and mechanical loading by skeletal muscle on bone stimulates and strengthens the bone [11,13]. Moreover, there are many common contributors both for muscle and bone such as sex hormones, growth factors, inflammatory cytokines and oxidative stress [1]. Therefore, age-related changes of those factors might influence both bone and muscle simultaneously [14,15]. Furthermore, it is believed that skeletal muscles secrete factors which affect bone directly, and vice versa [9,16]. In other words, there is direct communication between bone and muscle and it could contribute to strong relationship between bone and muscle.

However, mode or direction of dynamic loading of muscle on the bone is quite distinct according to the bone site [10,17]. Furthermore, cortical bone or trabecular bone, and bones in males and females show different age patterns, indicating earlier and constantly slow bone loss in men, but later and accelerated bone loss in women [18,19]. Therefore, the impact of muscle on bone might also differ according to the bone site or gender.

In the present study we clarified the relationship between muscle loss and osteoporosis in the Korean elderly. Moreover, we also investigated whether this relationship could be different according to gender and bone site.

2. Materials and methods

2.1. Study design and participants

The KNHANES is a nationwide, population-based, cross-sectional study, and has been conducted periodically since 1998 by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention to assess the health and nutritional status of the civilian, non-institutionalized Korean population. A stratified, multi-stage probability sampling design was used for the selection of household units. The KNHANES IV was conducted from 2007 to 2010 and data acquired for this study were part of the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV) 2009. Among the survey participants, elderly males and females over the age of 65 years were included for analysis and the values of healthy adults 20–39 years of age (974 males, 1241 females) were used as reference. Subjects with any pathological disorders (such as cancer, hyperthyroidism, malabsorption, renal failure, or hepatic failure) or taking medications known to alter calcium and bone metabolism (such as corticosteroids, heparin, or anticonvulsants) were excluded from the analysis. The subjects who used antiresorptive agents such as raloxifene, bisphosphonate, or hormone replacement therapies were also excluded.

2.2. Body composition and bone densitometry

Whole body and regional body composition were measured by dual energy x-ray absorptiometry as previously described (DXA, Discovery W, Hologic, Waltham, MA, USA) [20] following the manufacturer's protocol. Appendicular skeletal muscle mass (ASM) was calculated as the sum of lean soft tissue in bilateral upper and lower limbs, and relative ASM (RASM) was calculated as ASM adjusted by height-squared (ASM/height^2) [2,21]. The scanner determined total fat mass (TFM) in kg and relative total fat mass (RTFM) was calculated as TFM/height^2. Bone was scanned at the lumbar spine, femur neck and total hip in the posteroanterior projection using DXA equipment. Osteoporosis was defined as a BMD t-score −2.5 or below and T-scores were calculated using reference ranges for Asian populations provided by the manufacturer.

2.3. Data analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (PASW statistics) software (version 18, SPSS Inc., Chicago, IL, USA). Data are represented as mean ± standard deviation (SD). Pearson's correlation coefficient was calculated to analyze relationships between anthropometric parameters and BMD or age. Odds ratios (ORs) with 95% confidence intervals (CIs) for osteoporosis in each skeletal site were evaluated using the logistic regression analysis with or without adjustment for age and

Table 1
Baseline characteristics of study elderly and healthy young reference group (20–39 years).

	Study subjects (Age ≥ 60 years old)		Young reference group (20–39 years old)	
	Men	Women	Men	Women
N	711	847	974	1241
Age, years	72.4 ± 5.5	73.1 ± 5.9	30.7 ± 5.5	30.9 ± 5.5
Height, cm	164.5 ± 5.8	150.2 ± 5.9	173.5 ± 5.8	160.3 ± 5.5
Weight, kg	62.4 ± 9.7	54.4 ± 8.9	72.4 ± 11.6	57.0 ± 9.9
BMI, kg/m^2	23.0 ± 2.9	24.1 ± 3.4	24.0 ± 3.5	22.2 ± 3.7
aLM, kg/m^2	20.5 ± 2.9	14.2 ± 1.9	25.3 ± 3.5	15.9 ± 2.4
RASM, kg/m^2	7.53 ± 0.87	6.27 ± 0.66	8.41 ± 0.95	6.16 ± 0.79
Total fat mass, kg	14.1 ± 4.9	18.4 ± 5.6	–	–
RTFM, kg/m^2	5.2 ± 1.7	8.1 ± 2.3	–	–
Lumbar spine			–	–
BMD, g/cm^2	0.919 ± 0.170	0.742 ± 0.134	–	–
T-score	−0.9 ± 1.4	−2.3 ± 1.2	–	–
Femur neck			–	–
BMD, g/cm^2	0.695 ± 0.115	0.554 ± 0.093	–	–
T-score	−1.2 ± 0.9	−2.3 ± 0.9	–	–
Total Hip			–	–
BMD, g/cm^2	0.883 ± 0.128	0.712 ± 0.110	–	–
T-score	−0.4 ± 0.9	−1.2 ± 0.9	–	–
Osteoporosis, n (%)	90 (13.8%)	453 (60.3%)	–	–
Osteoporotic hip fracture, n (%)	13 (2.3%)	66 (22.3%)	–	–

BMI, body mass index; RASM, relative appendicular skeletal muscle; BMD, bone mineral density.

BMI according to decrease of RASM by 1 SD compared to the healthy reference group.

3. Results

The clinical characteristics of the study subjects and reference group are shown in Table 1. A total of 711 males and 847 females over the age of 65 years were included in the study group and the data from healthy adults (974 males and 1241 females) 20−39 years of age were used as reference levels. The prevalence of subjects who had been diagnosed as hypertension was 46.4% and type 2 diabetes mellitus was 17.0% in this study subjects.

3.1. Age patterns of muscle mass in elderly males and females

The RASM decreased with age (Fig. 1). However, the age patterns of RASM showed differences between males and females with more rapid loss in elderly males than in elderly females. Generally, 2.8−6.5% of muscle mass loss was observed in males, but only 2.5−3.8% was observed in females every decade (Fig. 1). After 75 years of age, males and females showed a similar amount of muscle loss, but males showed 2 times faster skeletal muscle loss from the seventh to eighth decade of life. Regarding correlation between age and variables for body composition, RASM showed negative correlation with age both in males and females ($r = -0.333$, $p < 0.001$ for males, $r = -0.180$, $p < 0.001$ for females). However, RTFM showed negative correlation only in females ($r = -0.104$, $p < 0.05$). BMI also correlated negatively with age both in males and females, but the correlation was weaker than with RASM (Table 2).

3.2. Relationship between muscle and bone

Table 3 presents the correlation between body composition parameters and BMD of each bone site. After adjusting for the significant confounding variables of bone, age, and BMI, RASM was positively related with BMD of the femur neck with a stronger relationship in males than females ($r = 0.207$, $p < 0.001$ for males, $r = 0.095$, $p < 0.05$ for females). This pattern was similarly observed in total hip BMD ($r = 0.237$, $p < 0.001$ for males, $r = 0.116$, $p < 0.05$ for females). In contrast, body fat parameters and RTFM, showed negative correlation with the femur neck and total hip BMD both in males and females ($r = -0.189$, $p < 0.001$ for males, $r = -0.196$, $p < 0.001$ for females). However, lumbar spine BMD in both males and females did not show any significant associations with these two body composition parameters.

Table 2
Correlation analysis between age and body composition in the elderly.

	Males	Females
RASM	−0.333[b]	−0.180[b]
RTFM	0.058	−0.104[a]
BMI	−0.192[b]	−0.141[b]

Values mean correlation coefficients (r) calculated using the Pearson correlation analysis.
[a]$p < 0.05$, [b]$p < 0.001$.
RASM, relative appendicular skeletal muscle; RTFM, relative total fat mass; BMI, body mass index.

Table 3
Partial correlation analysis between body composition and BMD adjusted for age and BMI.

	Lumbar Spine BMD, g/cm^2		Femur Neck BMD, g/cm^2		Total Hip BMD, g/cm^2	
	Males	Females	Males	Females	Males	Females
RASM, kg/m^2	0.029	0.053	0.207[b]	0.095[a]	0.237[b]	0.116[a]
RTFM, kg/m^2	−0.044	0.058	−0.189[b]	−0.092[a]	−0.196[b]	−0.091[a]

Values mean correlation coefficients (r) calculated using the Partial correlation analysis after adjusting for age and BMI.
[a]$p < 0.05$, [b]$p < 0.001$.
BMI, body mass index; ASM, appendicular skeletal muscle; RTFM, relative total fat mass; RASM, relative appendicular skeletal muscle; BMD, bone mineral density.

The results of the logistic regression for osteoporosis expressed as a decrease of risk per increase of RASM by 1 SD of the same sex healthy reference group are shown in Fig. 2. The higher RASM was generally associated with lower risk of osteoporosis. Before crude adjustment (model 1) and adjusting for age only (model 2), an increase of RASM showed significant risk reductions for all skeletal sites both in males and females. In model 3, the age- and BMI-adjusted OR for osteoporosis was 0.42 (95% CI 0.12−0.76) in the femur neck and 0.24 (95% CI 0.07−0.76) in total hip for males. Among females, the age- and BMI-adjusted OR for osteoporosis (0.65) showed importance only in total hip (95% CI 0.33−1.00). The degree of risk

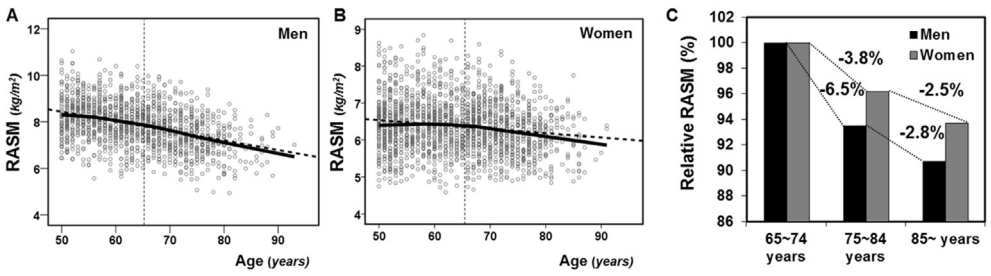

Fig. 1. Age-related changes of RASM (ASM/ht^2) for males (A) and females (B), and RASM across the decades in both males and females (C) in the elderly. The solid line (–) denotes the lowest curve and the dashed line (–) denotes the correlation line. RASM, relative appendicular skeletal muscle.

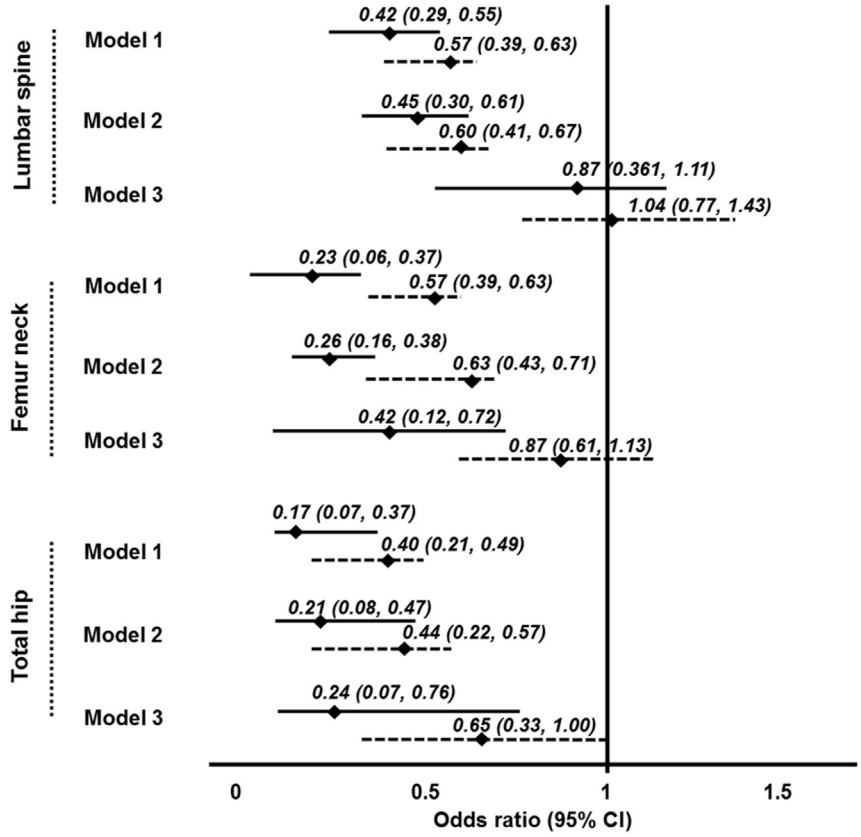

Fig. 2. Crude and adjusted odds ratios (ORs) with 95% confidence interval (CI) for osteoporosis according to 1 SD increase of RASM at each skeletal site. The solid line (–) denotes males and the dashed line (–) denotes females. Model 1: Crude. Model 2: Age-adjusted. Model 3: Age- and BMI-adjusted. RASM, relative appendicular skeletal muscle.

reduction for osteoporosis by increased muscle mass was higher in males than in females, and higher in total hip than in lumbar spine.

4. Discussion

In this nationally representative study, we demonstrated that higher RASM was significantly associated with lower risk for osteoporosis. However, these positive effects of muscle mass on bone showed differences according to the skeletal site or gender. The femur neck and total hip appeared to be more likely positively affected by muscle loading. Moreover, because males showed faster muscle loss with aging than females, the bones in males may be more prone to the favorable effects of muscle.

Progressive decline of skeletal muscle mass is a serious change associated with aging [22]. Sarcopenia is a pathological muscle mass loss leading to decreased strength and functional impairment [4,23]. Muscles play various important roles in the human body; thus loss of muscle mass can cause diverse functional and metabolic derangements in the elderly [24–26]. Muscle stimulates and strengthens bone through the dynamic loading on bone [11,12]. Therefore, sarcopenia is thought to decrease BMD and bone strength, and increase fracture risk [25,27–29].

In the sex-specific associations between RASM and bone in the present study, the correlation in males was stronger than in females. Sex hormones, growth hormones, nutritional balance and daily activity are conclusive factors for muscle quantity and quality. Therefore, differences in changes of those factors with aging in men and women might cause the gender-differences between bone and muscle [30,31]. However, biological mechanism which could underlie these gender differences is still unclear and needs to be further elucidated.

In the present study, risk reduction for osteoporosis in the femur neck and total hip with increased RASM was higher than in the lumbar spine. Muscle stimulates lumbar mainly via axial compression, but femur via compression, bending and torsion [17]. Accordingly, these differences in loading mode of muscle on the lumbar spine and the femur neck or total hip could contribute the site-specific associations between those two skeletal areas.

Muscle-bone crosstalk is very complex and the molecular mechanisms remain unclear [32]. However, numerous epidemiology data have shown the close relationship between osteoporosis and sarcopenia [29,33]. Furthermore, a recent study reported that muscle-related gene polymorphisms had significant associations with fracture risk and bone loss [33]. Based on these results showing the existence of shared pathogenesis in the age-related pathological conditions, osteoporosis, and sarcopenia could be expected. If a single therapeutic modality for maintaining bone and muscle is developed, it

could have significant potential for preventing fractures in the elderly.

This study has several limitations. First, the design was cross-sectional, and thus was limited to investigate whether higher muscle mass has a protective effect for future age-related bone loss. To verify the muscle as a therapeutic target for osteoporosis, a longitudinal study with an interventional design is necessary. Second, muscle strength was not assessed and therefore a relationship between muscle mass and strength or between muscle strength and bone could not be determined. Third, the levels of sex hormone and growth hormone which could affect both bone and muscle were not measured in this study. Finally, the number of hip fractures was very small, thus we could not analyze the association between the hip fracture risk and sarcopenia.

In conclusion, RASM has a significant relationship with BMD and sarcopenia is an independent risk factor for osteoporosis. Furthermore, the effects of muscle on bone appear stronger in males than in females and in the femur than in the lumbar. Intensive and constant physical activity for preventing muscle loss and engaging muscle strength could be a helpful therapeutic approach for preventing pathological bone loss, especially in the femur of elderly males.

Conflict of interest

All authors state that they have no conflict of interest.

References

[1] Doherty TJ. Invited review: aging and sarcopenia. J Appl Physiol (1985) 2003;95:1717−27.
[2] Arango-Lopera VE, Arroyo P, Gutierrez-Robledo LM, Perez-Zepeda MU, Cesari M. Mortality as an adverse outcome of sarcopenia. J Nutr Health Aging 2013;17:259−62.
[3] Kim TN, Park MS, Lim KI, Yang SJ, Yoo HJ, Kang HJ, et al. Skeletal muscle mass to visceral fat area ratio is associated with metabolic syndrome and arterial stiffness: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Res Clin Pract 2011;93:285−91.
[4] Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Sarcopenia in the elderly: diagnosis, physiopathology and treatment. Maturitas 2012;71:109−14.
[5] Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Curr Top Dev Biol 2005;68:123−48.
[6] Woo J, Leung J, Morley JE. Defining sarcopenia in terms of incident adverse outcomes. J Am Med Dir Assoc 2015;16:247−52.
[7] Cederholm T, Cruz-Jentoft AJ, Maggi S. Sarcopenia and fragility fractures. Eur J Phys Rehabil Med 2013;49:111−7.
[8] Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011;12:249−56.
[9] Tarantino U, Baldi J, Celi M, Rao C, Liuni FM, Iundusi R, et al. Osteoporosis and sarcopenia: the connections. Aging Clin Exp Res 2013;25(Suppl. 1):S93−5.
[10] Bouxsein ML. Determinants of skeletal fragility. Best Pract Res Clin Rheumatol 2005;19:897−911.
[11] Frost HM. Bone “mass” and the “mechanostat”: a proposal. Anat Rec 1987;219:1−9.
[12] Ashe M, Fehling P, Eng J, Khan K, McKay H. Bone geometric response to chronic disuse following stroke: a pQCT study. J Musculoskelet Neuronal Interact 2006;6:226.
[13] Ellman R, Spatz J, Cloutier A, Palme R, Christiansen BA, Bouxsein ML. Partial reductions in mechanical loading yield proportional changes in bone density, bone architecture, and muscle mass. J Bone Miner Res 2013;28:875−85.
[14] Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, Eldrup E, Dela F, et al. Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mech Ageing Dev 2003;124:495−502.
[15] Fulle S, Protasi F, Di Tano G, Pietrangelo T, Beltramin A, Boncompagni S, et al. The contribution of reactive oxygen species to sarcopenia and muscle ageing. Exp Gerontol 2004;39:17−24.
[16] Jahn K, Lara-Castillo N, Brotto L, Mo CL, Johnson ML, Brotto M, et al. Skeletal muscle secreted factors prevent glucocorticoid-induced osteocyte apoptosis through activation of beta-catenin. Eur Cell Mater 2012;24:197−209. discussion 209−10.
[17] Silva MJ. Biomechanics of osteoporotic fractures. Injury 2007;38(Suppl. 3):S69−76.
[18] Kim KM, Lim JS, Kim KJ, Choi HS, Rhee Y, Oh HJ, et al. Dissimilarity of femur aging in men and women from a Nationwide Survey in Korea (KNHANES IV). J Bone Miner Metab 2013;31:144−52.
[19] Warming L, Hassager C, Christiansen C. Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 2002;13:105−12.
[20] Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 2002;76:378−83.
[21] Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr 1990;52:214−8.
[22] Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 1999;107:123−36.
[23] Kim JH, Lim S, Choi SH, Kim KM, Yoon JW, Kim KW, et al. Sarcopenia: an independent predictor of mortality in community-dwelling older Korean men. J Gerontol A Biol Sci Med Sci 2014;69:1244−52.
[24] Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? Diabetes Care 2005;28:2541−2.
[25] Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889−96.
[26] Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. Int J Epidemiol 2007;36:228−35.
[27] Verschueren S, Gielen E, O'Neill TW, Pye SR, Adams JE, Ward KA, et al. Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men. Osteoporos Int 2013;24:87−98.
[28] Wu CH, Yang KC, Chang HH, Yen JF, Tsai KS, Huang KC. Sarcopenia is related to increased risk for low bone mineral density. J Clin Densitom 2013;16:98−103.
[29] Samu S, Juha S, Toni R, Risto H, Heikki K, Sirola J. Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia. Maturitas 2013;75:175−80.
[30] Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335:1−7.
[31] Philippou A, Maridaki M, Halapas A, Koutsilieris M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. In Vivo 2007;21:45−54.
[32] Kaji H. Interaction between muscle and bone. J Bone Metab 2014;21:29−40.
[33] Harslof T, Frost M, Nielsen TL, Husted LB, Nyegaard M, Brixen K, et al. Polymorphisms of muscle genes are associated with bone mass and incident osteoporotic fractures in Caucasians. Calcif Tissue Int 2013;92:467−76.