

博士學位論文

閉経後女性において、筋力は筋肉量とは
独立して骨の健康状態と関連している：
Japanese population-based osteoporosis study

近畿大学大学院
医学研究科医学系専攻
立木隆広

Doctoral Dissertation

Muscle strength is associated with bone health
independently of muscle mass in postmenopausal women :
the Japanese population-based osteoporosis study

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Department of Epidemiology and Healths Science, Major in Medical Sciences
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Muscle strength is associated with bone health independently of muscle mass in postmenopausal women: the Japanese population-based osteoporosis study

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Abstract

There are conflicting reports on whether muscle strength is associated with bone mineral density (BMD) independently of muscle mass. Here, we examined the association between muscle strength and BMD in a representative population of Japanese women. Cross-sectional data from 680 postmenopausal women, who were participants in the 15th-year follow-up survey of the Japanese Population-based Osteoporosis cohort study, were analyzed. Areal BMD (aBMD) at the femoral neck and lumbar spine, whole-body bone mineral density, and appendicular skeletal muscle mass (ASM, kg) were measured by dual-energy X-ray absorptiometry. The ASM index (ASMI, kg/m²) was calculated as ASM divided by height squared (m²). Grip strength (kg) was measured as an indicator of muscle strength. Grip strength showed significantly ($P < 0.05$) positive relationships with aBMDs at several skeletal sites after adjusting for ASMI and age (standardized partial regression coefficient (β) = 0.102 at femoral neck, $\beta = 0.126$ at lumbar spine). Adjusted means of aBMD at the femoral neck and lumbar spine showed significant increasing trends from the lowest to highest tertile of grip strength. Our findings indicate that muscle strength is associated with aBMD at several sites independently of muscle mass in Japanese postmenopausal women. Thus, postmenopausal women with strong muscle strength tend to have a healthy bone status regardless of muscle size.

Key words : Body composition, Epidemiology, Musculoskeletal system

Introduction

Muscle and bone play fundamental roles in human physiology: for example, they enable locomotion and movement, enhance blood flow to organs, and provide protection to vital organs ^[1]. The muscle–bone unit is the foundation of biological and life activities in humans, and numerous studies have examined the relationship between muscle and bone ^[2–7]. For instance, a number of studies have reported that greater muscle mass is associated with higher bone mineral density (BMD) ^[2, 3, 6, 7]. Lean soft tissue mass (LSTM) measured by dual-energy X-ray absorptiometry (DXA), a proxy of muscle mass ^[8, 9], is also positively associated with BMD ^[4]. On the other hand, sarcopenia, which is characterized by muscle volume loss and muscle dysfunction ^[10], often involves osteoporosis ^[5]. Sarcopenia increasingly occurs with advancing age ^[10], with a reported prevalence of up to 29% in community-dwelling elderly people ^[11]. Sarcopenia leads to adverse outcomes such as physical disability, poor quality of life, and death ^[10].

Mechanical loading by muscles is an essential mechanism for maintaining BMD ^[4, 12]. Muscle force and muscle weight (muscle mass), which are sources of mechanical loading, correlate with BMD ^[13]. Beneficial effects of exercise load on BMD have been reported by studies that compared these with sedentary behaviour ^[14]. Spaceflight, which is characterized by a lack of gravitational load on bones, reportedly leads to rapid bone loss of about 1–1.5% per month ^[15]. Given that mechanical loading by force and weight regulates bone mass ^[16], muscle strength (defined as the maximum amount of force that a muscle can exert ^[17]) may be related to BMD ^[18, 19]. It has been hypothesized that muscle strength is associated with BMD independently of muscle mass ^[20–22]. However, contradictory studies have reported that muscle strength is associated with BMD in a muscle mass-dependent manner ^[23, 24].

Thus, there is no empirical evidence, particularly that from epidemiological studies, concerning how muscle strength (maximum force) may affect BMD independently of muscle mass. In the present study, we sought to determine whether muscle strength is associated with BMD independently of muscle mass in a representative population of Japanese elderly women, and examined the individual impact of muscle strength and muscle mass on BMD.

Materials and methods

Study design and subjects

This study analyzed cross-sectional data from the Fifth Survey (the 15th-year follow-up survey) of the Japanese Population-based Osteoporosis (JPOS) cohort study, which was conducted in 2011 and 2012. Details of the JPOS cohort study are described elsewhere ^[25]. The JPOS cohort study was launched in 1996 to determine risk factors for osteoporotic fractures in Japanese women. The JPOS study areas comprised multiple municipalities to represent different environmental characteristics of Japan. Participants were randomly selected from 5-year age strata (15–79 years) according to inhabitant registries of the municipalities. The source population (accessible population) of the present study was 1800 women aged ≥ 35 years at the

First Survey in 1996 in four municipalities of JPOS cohort study areas, which included (1) Memuro Town, (2) Nishi-Aizu Town, (3) Joetsu City, and (4) Sangawa Town (Sanuki City) in Japan. Of the 1800 women, 1616 completed the First Survey and were invited to participate in the Fifth Survey. A total of 1063 women completed the Fifth Survey. After excluding 383 women who met the exclusion criteria, a total of 680 postmenopausal women formed the final study population (Fig. 1). Exclusion criteria were premenopausal status, history or present condition affecting bone metabolism or LSTM including hyperthyroidism, rheumatoid arthritis, myasthenia gravis, and menopause resulting from surgery. Participants without grip strength (kg) or areal bone mineral density (aBMD, g/cm²) data were also excluded. All participants provided written informed consent before participating in the follow-up survey. The study protocol was approved by the Ethics Committee of the Kindai University Faculty of Medicine.

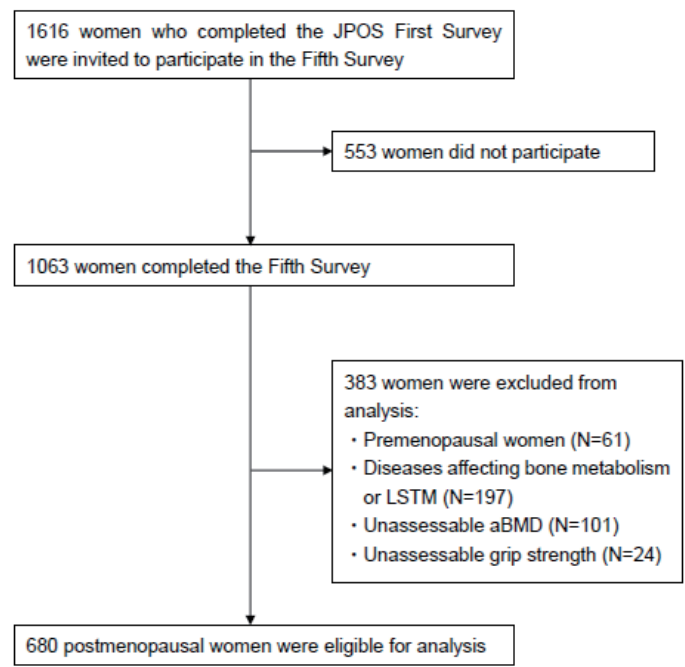


Fig. 1. Flow diagram of subject selection. LSTM, lean soft tissue mass.

aBMD and appendicular skeletal muscle mass index

Both aBMD and body composition parameters were determined with a single DXA scanner (QDR-4500A; Hologic, Bedford, MA, USA) mounted on a mobile examination car. A single experienced radiologic technologist performed all scans. aBMD was measured at the femoral neck and at L2 to L4 of the lumbar spine. LSTM and aBMD of the whole-body were measured at the same time. LSTM was divided into defined regions, i.e., the arms, legs, and trunk. Arm and leg LSTM were isolated from trunk LSTM using the standard manufacturer-recommended analysis. In anterior whole-body images, the arms were delineated at the vertical shoulder line bisecting the heads of the humerus at the glenoid fossa, and legs were separated by two angled lines, which composed a pelvic triangle with a horizontal line at the crest of the ilium and bisected the two

femoral necks ^[26]. Appendicular skeletal muscle mass (ASM, kg) was calculated as the sum of arm and leg LSTM volumes. The height-normalized index of ASM (appendicular skeletal muscle mass index, ASMI; kg/m²) was calculated as ASM divided by height squared (m²) ^[8], and was used as an index of muscle mass ^[10]. The in vivo reproducibility of aBMD ^[25] and LSTM, represented by coefficients of variation (CV), was 1.04% for aBMD at the lumbar spine, 1.10% for aBMD at the femoral neck, 1.06% for LSTM, and 1.37% for ASM.

Assessment of muscle strength

Grip strength, used to assess muscle strength, was measured with a digital hand dynamometer (TKK5101; Takei Kagaku, Tokyo, Japan) by trained physical therapists. Participants received the same degree of explanation and verbal encouragement from the physical therapists. In the upright position, participants spread both legs naturally with their elbows extended and gripped the dynamometer tightly with maximum effort. Grip strength was measured twice each for both right and left hands. The mean value of the best performances of both sides was used in the analyses. Reproducibility of grip strength, represented by CV, was 3.62%.

Body size measurements

Height (cm) and weight (kg) were measured with an automatic scale (TK-11868h; Takei Kagaku, Tokyo, Japan). Body mass index (BMI) was calculated as weight divided by height squared (kg/m²).

Interviews

Detailed interviews were conducted by trained nurses using a structured questionnaire. Items included questions about menstrual history, current and past gynecological conditions, history of fracture, and other conditions or medications that could affect bone metabolism and LSTM.

Statistical analysis

Subjects were divided into three tertile classes by grip strength. Simple regression analysis was used to examine the trend from the lowest to highest tertile of grip strength. Pearson's correlations were used to examine relationships between grip strength and ASMI and between ASMI and age. To evaluate associations between grip strength and aBMD that are independent of ASMI, multiple regression analysis was performed, with grip strength and ASMI used in the same model as independent variables. Adjusted mean values for each aBMD, stratified by grip strength, were calculated using the general linear model after adjusting for ASMI and age. Multiple linear regression analysis was also used to test trends of the mean values from the lowest tertile group to the highest tertile group of grip strength after adjusting for ASMI and age. All data analyses were performed with SPSS (version 22.0J; SPSS, Tokyo, Japan). Statistical significance was defined as $P < 0.05$ for all tests.

Results

A total of 1063 women participated in the Fifth Survey. Of these, data from 680 subjects who did not meet the exclusion criteria were analyzed (Fig. 1). Table 1 shows characteristics of the study subjects classified by tertile of grip strength. The trend test showed a significant decrease in mean age from the lowest tertile to the highest tertile of grip strength. There was a significant increase in ASMI from the lowest tertile to the highest tertile of grip strength. Table 2 shows relationships among age, grip strength, and ASMI. Grip strength showed a significant inverse relationship with age, and significant positive relationships with ASMI and BMI. aBMDs for the whole-body, femoral neck, and lumbar spine also showed a significant increase from the lowest tertile to the highest tertile of grip strength (Table 1).

Table 3 shows the individual impact of grip strength on aBMD and that of ASMI on aBMD. There were significant positive relationships between grip strength and aBMD for the whole-body, femoral neck, and lumbar spine (Model 1), and between ASMI and aBMDs (Model 2). When grip strength and ASMI were considered in the same multiple linear regression model, grip strength still showed significant positive relationships with aBMD at the femoral neck and lumbar spine (Models 3–5). On the other hand, no significant relationships were observed between grip strength and whole-body aBMD in Models 4 and 5.

Table 1. Subject characteristics classified by grip strength.

	All subjects n=680	Tertile classes of grip strength			Trend from T1 to T3 of grip strength	
		T1 n=225	T2 n=228	T3 n=227	β	P-value
Grip strength (kg)	21.3 \pm 4.7	16.1 \pm 2.6	21.3 \pm 1.2	26.3 \pm 2.5		
Age (years)	67.9 \pm 10.1	73.3 \pm 9.8	67.1 \pm 9.7	63.2 \pm 8.0	-0.41	<0.001
Height (cm)	151.3 \pm 6.6	147.2 \pm 6.3	151.2 \pm 5.7	155.5 \pm 4.8	0.51	<0.001
Weight (kg)	51.7 \pm 8.6	48.0 \pm 7.6	51.5 \pm 8.3	55.5 \pm 8.2	0.36	<0.001
BMI (kg/m ²)	22.5 \pm 3.4	22.1 \pm 3.4	22.5 \pm 3.4	23.0 \pm 3.2	0.10	0.009
ASM (kg)	14.9 \pm 2.0	13.7 \pm 1.6	14.8 \pm 1.7	16.3 \pm 1.8	0.51	<0.001
ASMI (kg/m ²)	6.51 \pm 0.67	6.34 \pm 0.66	6.48 \pm 0.67	6.72 \pm 0.63	0.23	<0.001
Whole-body aBMD (g/cm ²)	0.840 \pm 0.096	0.806 \pm 0.083	0.842 \pm 0.102	0.871 \pm 0.091	0.27	<0.001
Femoral neck aBMD (g/cm ²)	0.624 \pm 0.109	0.573 \pm 0.101	0.630 \pm 0.103	0.669 \pm 0.102	0.36	<0.001
Lumbar spine aBMD (g/cm ²)	0.838 \pm 0.146	0.780 \pm 0.130	0.839 \pm 0.139	0.893 \pm 0.146	0.32	<0.001

n, number; BMI, body mass index; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; aBMD areal bone mineral density; T, tertile; β , standardized regression coefficient.

ASMI was calculated as appendicular skeletal muscle mass divided by height squared. Values represent mean \pm standard deviation. Simple regression analysis was used to examine the trend from the lowest (T1) to highest (T3) tertile of grip strength.

The dependent variable was each value of measurement, and the independent variable was the tertile class of grip strength. P < 0.05 was considered statistically significant.

Mean values of aBMD in each tertile group of grip strength adjusted for ASMI and age are shown in Fig. 2. aBMD at the femoral neck showed a significant increasing trend from the lowest to highest tertile of grip strength. aBMD at the lumbar spine also showed a significant increasing trend from the lowest to highest tertile of grip strength.

Table 2. Relationships among grip strength, ASMI, BMI, and age.

	ASMI		BMI		Age	
	r	P-value	r	P-value	r	P-value
Grip strength	0.232	<0.001	0.102	0.008	-0.478	<0.001
ASMI			0.725	<0.001	0.049	0.206
BMI					0.004	0.926

ASMI, appendicular skeletal muscle mass index; BMI, body mass index.
Pearson's correlations were assessed using data from 680 women.

Table 3. Individual impact of grip strength on aBMD and that of ASMI on aBMD.

Independent variables in the model	Dependent variables					
	Whole-body aBMD		Femoral neck aBMD		Lumbar spine aBMD	
	β	P-value	β	P-value	β	P-value
Model 1						
Grip strength	0.295	<0.001	0.387	<0.001	0.347	<0.001
Model 2						
ASMI	0.129	0.001	0.235	<0.001	0.216	<0.001
Model 3						
Grip strength	0.280	<0.001	0.351	<0.001	0.313	<0.001
ASMI	0.064	0.088	0.153	<0.001	0.144	<0.001
Model 4						
Grip strength	0.043	0.277	0.102	0.006	0.126	0.002
ASMI	0.141	<0.001	0.235	<0.001	0.205	<0.001
Age	-0.458	<0.001	-0.483	<0.001	-0.363	<0.001
Model 5						
Grip strength	0.051	0.205	0.132	<0.001	0.152	<0.001
ASMI	0.091	0.074	0.037	0.424	0.037	0.468
Age	-0.452	<0.001	-0.460	<0.001	-0.343	<0.001
BMI	0.067	0.174	0.261	<0.001	0.223	<0.001

aBMD, areal bone mineral density; ASMI, appendicular skeletal muscle mass index; BMI, body mass index; β , standardized regression coefficient.
Simple or multiple regression analysis was performed using data from 680 women.

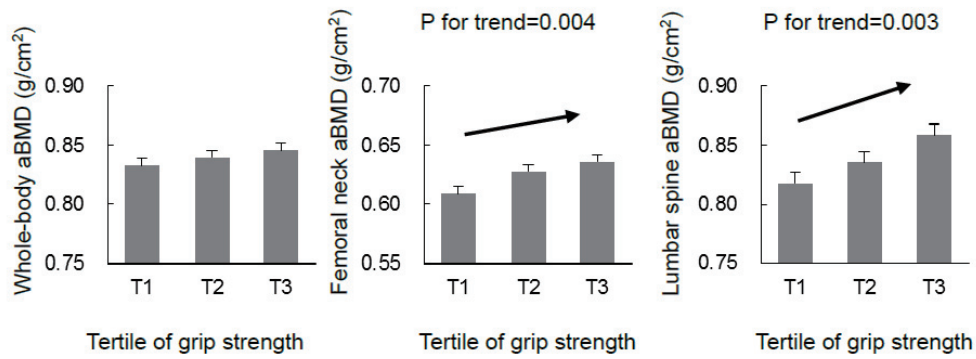


Fig. 2. Means and standard errors of areal bone mineral density (aBMD) in each tertile (T1 < T2 < T3) group of grip strength adjusted for appendicular skeletal muscle mass index and age. Appendicular skeletal muscle mass index was calculated as appendicular skeletal muscle mass divided by height squared. Arrows show significant trends ($P < 0.05$).

Discussion

In the present study, which targeted Japanese postmenopausal women, we found that grip strength was associated with BMD at the femoral neck and lumbar spine, and that these associations were independent of the relationship between muscle mass and BMD. Elderly women who have strong grip strength tended to have higher BMD regardless of muscle mass. This finding suggests that muscle strength impacts BMD independently of muscle size, and that the maximum force of muscle is a modulator of bone regulation in elderly women.

On the other hand, grip strength showed no significant relationship with whole-body BMD after adjusting for muscle mass and age in the present study. Rajaei et al. [27] reported a significant difference between mean whole-body BMD and local measurements, such as BMD at the lumbar spine and hip. Therefore, whole-body BMD and local measurements may have various relationships with grip strength.

There are conflicting reports in the literature regarding the association between muscle strength and BMD. A study of elderly Caucasian women reported that quadriceps strength was associated with BMD at the femoral neck independently of lean mass [20]. Moreover, a study from three diverse populations consisting of African American, Caucasian, and Chinese women also found an independent association between grip strength and BMD [21]. These reports suggest that muscle strength, which is the maximum force of muscle [17], impacts bone health independently of muscle size. In contrast, a study from two communities in the United States concluded that muscle mass is more strongly related to hip BMD than quadriceps strength [24]. Furthermore, a study in Korea reported an association between muscle strength and BMD that was dependent on muscle mass [23]. These latter two studies did not find a significant independent effect of muscle strength on bone [23, 24], suggesting that the association between muscle strength and BMD is mediated by muscle mass.

The present study showed an association between grip strength and aBMD independently of muscle mass. Mechanical loading by muscle is an essential mechanism for maintaining BMD [4, 12]. The mechanical contribution of muscles to bone includes forces generated by muscle (muscle quality) as well as muscle weight (muscle mass). Given that muscle quality does not necessarily equal muscle mass, there must be an independent impact of muscle strength on bone. Skeletal muscle and bone are the two largest tissues of the musculoskeletal system. An interaction between muscle and bone was previously reported [16, 28, 29]. One explanation for the interaction is a mechanical coupling of bone and skeletal muscle [16]. For example, decreased mechanical loading by muscle atrophy (e.g., sarcopenia) induces bone loss [30, 31]. There are two components involved in mechanical loading on bone [21, 32]. One form of mechanical loading on bone is muscle force [12]. Muscle weight may also regulate bone mass via mechanical loading [4]. On the other hand, muscle force is thought to depend partially on muscle weight [23]; it is also reportedly independent of muscle weight [22]. Given that muscle strength is defined as the maximum amount of force [17], the present results suggest that mechanical contribution of muscle strength on bone is partly independent of muscle weight. Thus, the maximum force of muscle may modulate bone regulation along with the muscle force.

In contrast to the foregoing, some studies did not find a significant independent effect of muscle strength (maximum force) on bone [23, 24]. This may be due to differences in study design, such as differences in the study population and how muscle strength was measured. For instance, some studies measured leg/quadriceps strength to evaluate muscle strength [23, 24]. However, it has been reported that measurement of leg/quadriceps strength is less reliable than that of grip strength [33]. The present study has a number of strengths over previous studies. First, grip strength, which provides a highly reproducible measurement of muscle strength [33], was assessed in this study. Second, our sample size was sufficient to examine whether muscle strength is associated with BMD independently of muscle mass. Finally, we used DXA, which has high reproducibility, to measure aBMD and body composition [34].

The present study also has some limitations worth noting. First, although the study areas were scattered throughout Japan, we did not randomly select the areas from all municipalities in Japan [25]. Moreover, the study population accounted for 37.8% of the source population. These limitations may have introduced selection bias and affected our present results. However, the source population was the accessible population of the first survey of the JPOS study, conducted 15 years prior to the present study survey (the Fifth JPOS survey). The present study population included 64.0% of the participants of the Fifth JPOS survey. Moreover, BMI values of the study population (Table 1) did not differ from those reported in the Japan National Health and Nutrition Survey [35] (mean BMIs of Japanese women aged 50–59 years, 60–69 years, and ≥ 70 years were reported to be 22.4, 22.7, and 22.8 kg/m², respectively). Third, all results were obtained from cross-sectional analyses, and thus temporal relationships of the associations could not be investigated.

In Japanese postmenopausal women, grip strength was associated with BMD at several skeletal sites, independently of the relationship between ASMI and BMD. Elderly women with strong muscle strength

tended to have a healthy bone status regardless of muscle mass. The present results suggest that the maximum force of muscle is a modulator of bone regulation in elderly women.

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Compliance with ethical standards

Conflict of interest

The authors have no conflicts of interest to declare.

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