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ORIGINAL STUDY

The association between hormone therapy and sarcopenia in postmenopausal women: the Korea National Health and Nutrition Examination Survey, 2008-2011

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Abstract

Objective: Menopausal transition contributes to sarcopenia, but the effects of hormone therapy (HT) on sarcopenia in postmenopausal women have not been determined. This study assessed the effect of HT on sarcopenia in postmenopausal women.

Methods: The present study included 4,254 postmenopausal women who participated in the Korea National Health and Nutritional Examination Surveys from 2008 to 2011. Appendicular skeletal muscle mass divided by weight (ASM/Wt) and the prevalence of sarcopenia were analyzed in groups of women stratified by duration of HT use.

Results: ASM/Wt was higher and the prevalence of sarcopenia was lower in participants with a history of prolonged ($\geq$13 mo) HT use than in participants with a shorter duration of HT use or no HT use. After adjusting for multiple confounding factors, prolonged use of HT remained significantly associated with estimated mean ASM/Wt and the prevalence of sarcopenia (odds ratio: 0.60; 95% confidence interval: 0.41-0.88; $P = 0.01$). In addition, the prevalence of sarcopenia was linearly associated with history of hypertension, duration of hypertension, physical activity, and duration of HT use. Subgroup analysis showed that the association between duration of HT use and the prevalence of sarcopenia was maintained in younger (<65 y old) and leaner (body mass index <25 kg/m^2) postmenopausal women.

Conclusions: The present study showed that the prolonged use of HT was associated with high muscle mass and a low prevalence of sarcopenia in postmenopausal women.

Key Words: Appendicular skeletal muscle mass – Hormone therapy – Sarcopenia.

Sarcopenia is defined as a loss of skeletal muscle mass and strength, and is believed to mostly affect older individuals.[1] Muscle mass decreases with age, with a 0.5% to 1.0% reduction in muscle mass per year after 70 years of age.[2] Sarcopenia is present in about one quarter to one half of men and women older than 65 years,[3] but may occur earlier in life.[4] Sarcopenia is now considered a muscle disease causing adverse health outcomes due to low muscle mass and strength.[5] Sarcopenia increases the risks of falls, fractures, disability, and functional impairments, as well as mortality.[6-9] In addition, individuals with sarcopenia have higher insulin resistance and are at increased risk of diabetes and cardiovascular disease than nonsarcopenic individuals.[10-12] Because women have a longer lifespan than men, women are more likely to experience the negative muscular changes associated with aging.

The aging process is often accompanied by comorbid conditions that contribute to the development of sarcopenia.[13,14] Age-related reductions in anabolic hormones such as testosterone, growth hormone, and insulin-like growth factor-1 have been shown to be associated with muscle loss.[15,16] Although sarcopenia is highly prevalent in postmenopausal women,[17,18] whether decline of estrogen contributes to development of sarcopenia in postmenopausal women is not determined. Accelerated muscle loss is associated with the menopausal transition,[19,20] suggesting that hormone supplementation may prevent or reduce loss in muscle mass.[21] Studies assessing the association between hormone therapy (HT) use and muscle loss have, however, yielded inconsistent results.[20,22,23] To our knowledge, few large-scale studies have assessed the ability of HT use to attenuate muscle loss in

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postmenopausal women. The present study therefore evaluated whether the duration of HT use was associated with muscle mass and the prevalence of sarcopenia in postmenopausal women.

MATERIALS AND METHODS

Participants

This study was based on data from the Korea National Health and Nutrition Examination Survey (KNHANES) collected from 2008 to 2011. KNHANES is a cross-sectional, population-based, nationwide survey conducted by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention. Of the 20,698 participants who underwent dual-energy x-ray absorptiometry (DXA; QDR 4500A; Hologic Inc., Waltham, MA), 4,254 postmenopausal women were initially selected. After excluding participants with incomplete information on HT use, 4,233 postmenopausal women were enrolled, and the association between HT use and sarcopenia was assessed in this population. The KNHANES was approved by the Institutional Review Board of the KCDC (IRB No: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, and 2011-02CON-06C), and all participants provided written informed consent before participation.

Measurements of biochemical and clinical parameters

Appendicular skeletal muscle mass (ASM), defined as the sum of lean soft tissue mass (nonfat and nonbone mass) of the arms and legs, was measured using DXA.[24] DXA calibrations were maintained through an internal referencing system, which periodically measures bone and soft tissue equivalent reference standards during the examination of the participants. ASM/Wt was calculated as ASM divided by weight. Sarcopenia was defined as an ASM/Wt less than one standard deviation below the mean for healthy adults aged 20 to 39 years. The cut off value for sarcopenia in women was 25.6%.[11,25] Body mass and height were measured by trained staff, and body mass index (BMI) was calculated as body mass (kg) divided by height squared (m^2). Demographic and personal medical data were collected using standardized health questionnaires. The health interview was conducted by trained staff members, including physicians, medical technicians, and health interviewers. These data included reproductive factors (age at menarche, age at menopause, number of pregnancies, history of oral contraceptive [OC] use, and history of HT use), history of hypertension (HTN) and diabetes mellitus (DM), smoking history (current or ex-), and physical activity (walk/moderate/high). Nutrient status (total energy intake, protein intake, carbohydrate intake, and fat intake) was determined using a 24-hour dietary recall questionnaire.

Statistical analysis

All analyses were performed using the Complex Samples Plan in SPSS version 18.0 software (IBM, Armonk, NY) according to the KNHANES data analysis guidelines. The data were weighted, stratified, and clustered. The sample represents the total noninstitutionalized civilian population of Korea. Participants were stratified according to the duration of HT use (none, 1-12 mo, and $\geq$13 mo). The groups were compared in terms of demographic and clinical variables by using analysis of variance and Chi-square test. Complex Samples General Linear Model was used to evaluate the estimated mean of ASM and ASM/Wt among HT use groups. The association between HT use and the prevalence of sarcopenia was estimated using Complex Samples Logistic Regression. To assess which factors are independently associated with ASM/Wt and the prevalence of sarcopenia, Complex Samples General Linear Model, and Complex Samples Logistic Regression were used for analysis. All continuous data are presented as mean $\pm$ standard error, and all categorical data as unweighted numbers and weighted prevalence. $P < 0.05$ was regarded as statistically significant.

RESULTS

General characteristics of postmenopausal women stratified by duration of hormone therapy use

The general characteristics of participants are presented in Table 1. Of the 4,233 participants, 3,656 (86.4%) received no HT, 302 (7.1%) were treated with HT for 1 to 12 months (mean, 5.2 ± 0.28 mo), and 275 (6.5%) received HT for more than 13 months (mean, 52.8 ± 2.90 mo). Participants with a history of HT use were significantly younger than participants without a history of HT use. Mean BMI did not differ significantly among the three groups. Participants with a history of prolonged HT use were younger at menarche and older at menopause than participants in the other groups. Thus, duration of menstruation was significantly longer and duration of menopause was shorter in the prolonged HT use group. The number of pregnancies was lower in participants who received HT for 1 to 12 months than in participants who received no HT. History of OC use was significantly more frequent in participants with than without a history of HT use. Intake of nutrients, including intake of total energy, protein, carbohydrate, and fat, was significantly greater in participants with a prolonged history of HT use. Previous histories of DM and HTN were less frequent in participants who received HT for 1 to 12 months than in the other groups. The age of diagnosis of DM and HTN was older in non-HT users, but duration of DM and HTN was longer in non-HT users than in HT users. History of smoking and physical activity did not differ in the three groups. ASM and ASM/Wt were significantly higher, and the prevalence of sarcopenia was significantly lower, in participants with a prolonged history of HT use than in the other two groups.

Association between hormone therapy and appendicular skeletal muscle mass

After adjusting for multiple confounding factors, the estimated means of ASM and ASM/Wt were compared in the three groups of participants (Fig. 1). The model was adjusted for age, age at menarche, age at menopause, duration of

TABLE 1. *Demographic and characteristics of postmenopausal women stratified by duration of hormone therapy*

	No HT use ($n = 3,656$)	HT use for 1-12 mo ($n = 302$)	HT use for ≥13 mo ($n = 275$)	*P*
Age, y	64.5 ± 0.25	57.2 ± 0.69[a]	59.8 ± 0.48[a]	<0.01
BMI, kg/m^2	24.1 ± 0.07	23.7 ± 0.23	23.8 ± 0.18	0.07
Reproductive factors				
Age at menarche, y	16.0 ± 0.05	15.5 ± 0.14[a]	15.5 ± 0.13[a]	<0.01
Age at menopause, y	49.1 ± 0.10	48.7 ± 0.37	50.0 ± 0.42[b]	0.08
Duration of menstruation, y	33.1 ± 0.11	33.2 ± 0.39	34.4 ± 0.44[a]	0.02
Duration of menopause, y	15.0 ± 0.30	8.4 ± 0.56[a]	9.8 ± 0.48[a]	<0.01
Number of pregnancies, *n*	5.0 ± 0.05	4.5 ± 0.18[a]	5.0 ± 0.19	0.01
Past history of OC use, *n*	729 (20.0%)	95 (33.4%)[a]	88 (33.8%)[a]	<0.01
Duration of OC use, mo	20.7 ± 1.54	13.4 ± 2.52[b]	31.5 ± 7.05	0.01
Duration of HT use, mo	0	5.2 ± 0.28[a]	52.8 ± 2.90[a]	<0.01
Nutrient status				
Energy intake, kcal	1513.3 ± 15.51	1530.0 ± 46.33	1670.2 ± 46.68[a]	<0.01
Protein, g	50.3 ± 0.63	54.5 ± 2.23	59.7 ± 1.99[a]	<0.01
Carbohydrate, g	282.3 ± 3.00	276.8 ± 7.42	303.0 ± 8.83[b]	0.07
Fat, g	21.6 ± 0.49	24.6 ± 1.51	27.1 ± 1.22[a]	<0.01
Medical history				
DM, *n*	488 (13.5%)	26 (7.3%)[a]	27 (10.1%)	<0.01
Age at diagnosis with DM, y	58.6 ± 0.67	54.8 ± 1.46[b]	56.5 ± 1.87	0.05
Duration of DM, y	8.4 ± 0.40	6.7 ± 1.07	6.2 ± 1.10	0.07
HTN, *n*	1501 (40.4%)	107 (30.9%)[a]	93 (37.5%)	0.03
Age at diagnosis with HTN, y	60.2 ± 0.37	54.2 ± 0.91[a]	56.5 ± 0.94[a]	<0.01
Duration of HTN, y	7.9 ± 0.23	7.4 ± 0.73	6.2 ± 0.61[b]	0.03
Social history				
Smoking, *n* (current/ex-)	171/145 (5.5%/4.6%)	8/14 (2.9%/5.2%)	7/10 (3.9%/2.3%)	0.16
Physical activity, *n* (walk/moderate/high)	1444/483/387 (40%/12.7%/11.5%)	116/44/40 (37.7%/16.5%/14.3%)	112/32/33 (43.4%/12.4%/10.8%)	0.77
Sarcopenia				
ASM, kg	13.9 ± 0.05	14.2 ± 0.13[b]	14.6 ± 0.14[a]	<0.01
ASM/Wt, %	24.8 ± 0.08	24.8 ± 0.19	25.1 ± 0.17[b]	0.13
Sarcopenia, *n*	2303 (66.1%)	201 (64.4%)	165 (56.7%)[b]	0.09

Continuous variables are presented as mean ± standard error, and categorical variables as unweighted number (weighted prevalence).
ASM, appendicular skeletal muscle mass; ASM/Wt, appendicular skeletal muscle mass divided by weight; BMI, body mass index; DM, diabetes mellitus; HT, hormone therapy; HTN, hypertension; OC, oral contraceptive.
[a]$P < 0.01$.
[b]$P < 0.05$.

menstruation and menopause, number of pregnancies, history of OC use, duration of OC use, past history of DM and HTN, duration of HTN and DM, smoking history, physical activity, and nutrient intake (total, proteins, carbohydrates, and fats). The model showed lower ASM by category of self-reported HT use for 13 months or more (Fig. 1A). The estimated mean ASM/Wt was also significantly higher in participants who received HT for 13 months or more than in the other groups (Fig. 1B).

Association between hormone therapy and sarcopenia

Table 2 shows the odds ratios (ORs) and 95% confidence intervals (CIs) for sarcopenia. In an unadjusted model, the OR for sarcopenia was significantly lower in the group that received HT for 13 months or more than in the other groups (OR = 0.67; 95% CI, 0.47-0.95; $P < 0.05$). After adjustment for reproductive factors, medical history, social history, and nutrient factors, the association of HT use with the prevalence of sarcopenia was still significant (OR = 0.60; 95% CI, 0.41-0.88; $P = 0.01$).

Association of appendicular skeletal muscle mass and sarcopenia with variable factors

Table 3 presents multivariate analysis estimates, the association of multiple variables with ASM/Wt, and the prevalence of sarcopenia. History of DM, duration of DM, history of HTN, duration of HTN, smoking history, and physical activity were associated with ASM/Wt. In reproductive factors, history of HT use was associated with ASM/Wt, but duration of HT use was not associated with ASM/Wt. History of HTN, duration of HTN, and physical activity were independently associated with the prevalence of sarcopenia. In addition, duration of HT use was linearly associated with the prevalence of sarcopenia (OR = 0.994 per 1 mo; 95% CI, 0.989-0.999; $P = 0.02$).

Association between hormone therapy and sarcopenia in different subgroups

Evaluation of the association between the duration of HT use and the prevalence of sarcopenia in groups of participants differing by age and BMI (Table 4) showed that the ORs for sarcopenia in older participants (≥65 y) did not differ among the three HT use groups. In younger participants (<65 y); however, the OR for sarcopenia was significantly lower in the group that received HT for 13 months or more than in the group that did not receive HT. Regardless of BMI subgroup, the OR for sarcopenia was lower in participants who received prolonged treatment with HT than in participants who did not receive HT, but statistical significance was only observed in participants with BMI <25 kg/m^2.

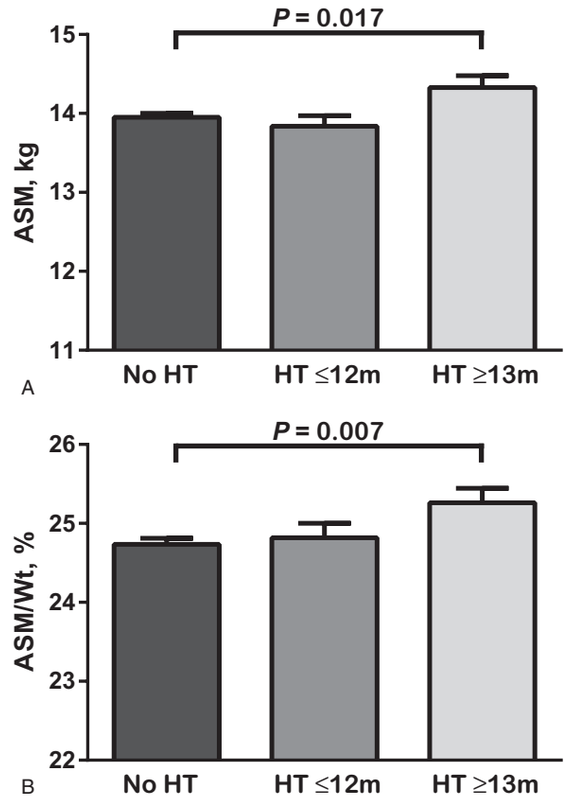

FIG. 1. Estimated means of (**A**) appendicular skeletal muscle mass and (**B**) appendicular skeletal muscle mass divided by weight in each hormone therapy group after adjusting for multiple confounding factors. Data were analyzed using Complex Samples General Linear Models and are expressed as mean ± standard error. Adjusted model: age, age at menarche, age at menopause, duration of menstruation and menopause, number of pregnancies, past history of OC use, duration of OC use, past histories of DM and HTN, duration of HTN and DM, smoking history, physical activity, and energy intake (total, proteins, carbohydrates, and fats). ASM/Wt, appendicular skeletal muscle mass divided by weight; DM, diabetes mellitus; HT, hormone therapy; HTN, hypertension; OC, oral contraceptive.

DISCUSSION

The present study showed that prolonged use of HT for 13 months or more was associated with high ASM/Wt and a low prevalence of sarcopenia in postmenopausal women. These associations were statistically significant in groups of postmenopausal women younger than 65 years and those with BMI less than 25 kg/m^2.

The mechanism by which estrogen contributes to the preservation of muscle mass has remained elusive.[22,26] Estrogen may be directly involved in muscle metabolism by binding to estrogen receptors expressed on skeletal muscle, as well as indirectly by altering the secretion of growth hormone and insulin growth factor 1.[27,28] Estrogen may also play a role in regulating carbohydrate and lipid metabolism by relieving muscle glycogen and inducing lipid oxidation, which may influence skeletal muscle composition in postmenopausal women.[29] Although use of HT enhances muscle strength,[20,30] few studies have found that use of HT increases muscle mass in postmenopausal women,[20,31,32] whereas most studies have not.[19,26,33] For example, a recent meta-analysis found that use of HT was not associated with muscle mass.[23] In the present study, prolonged use of HT correlated with muscle mass and with the prevalence of sarcopenia in postmenopausal women, even after adjusting for multiple confounding factors, including reproductive and nutrient factors.

The association between use of HT and muscle mass was also analyzed in subgroups of postmenopausal women stratified by age and BMI. Although ORs were lower in all age and BMI subgroups that received HT for 13 months or more, statistical significance was observed only in postmenopausal women younger than 65 years or with BMI less than 25 kg/m^2. These results suggest that the beneficial effects of HT use on sarcopenia may be more prominent in younger and leaner postmenopausal women. ORs of sarcopenia in participants with prolonged use of HT were, however, decreased, regardless of age and BMI, and the subgroups showing statistical significance included more participants with a history of HT use. Thus, the number of participants in these subgroups who

TABLE 2. *Odds ratios for the prevalence of sarcopenia in postmenopausal women stratified by duration of hormone therapy*

	No HT use ($n = 3,656$)	HT use for 1-12 mo ($n = 302$)	HT use for ≥ 13 mo ($n = 275$)	P for trend
Unadjusted	1 (ref)	0.93 (0.68-1.27)	0.67 (0.47-0.95)[b]	0.03
Model 1	1 (ref)	0.95 (0.69-1.31)	0.64 (0.45-0.92)[b]	0.03
Model 2	1 (ref)	0.93 (0.68-1.28)	0.60 (0.41-0.88)[b]	0.02
Model 3	1 (ref)	0.90 (0.66-1.24)	0.59 (0.40-0.87)[a]	0.01
Model 4	1 (ref)	0.89 (0.65-1.23)	0.60 (0.41-0.88)[b]	0.01

Data were analyzed using Complex Samples Logistic Regression and are expressed as odds ratio (95% confidence interval).
Model 1: adjusted for age, age at menarche, age at menopause, and number of pregnancies.
Model 2: adjusted for age, age at menarche, age at menopause, number of pregnancies, past history of OC use, past histories of DM and HTN, smoking history, and physical activity.
Model 3: adjusted for age, age at menarche, age at menopause, number of pregnancies, past history of OC use, past histories of DM and HTN, smoking history, physical activity, and energy intake (total, proteins, carbohydrates, and fats).
Model 4: adjusted for age, age at menarche, age at menopause, duration of menstruation and menopause, number of pregnancies, past history of OC, duration of OC use, past histories of DM and HTN, duration of HTN and DM, smoking history, physical activity, and energy intake (total, proteins, carbohydrates, and fats).
DM, diabetes mellitus; HT, hormone therapy; HTN, hypertension; OC, oral contraceptive.
[a] $P < 0.01$.
[b] $P < 0.05$.

TABLE 3. *The association of appendicular skeletal muscle divided by weight and prevalence of sarcopenia with multiple variables*

	ASM/Wt		Sarcopenia	
	B (*t* value)	*P*	ORs	*P*
Age, y	0.014 (0.486)	0.63	1.001 (0.957-1.048)	0.96
Nutrient status				
Energy intake, kcal	0.001 (1.721)	0.09	0.999 (0.997-1.000)	0.06
Protein intake, g	−0.007 (−1.508)	0.13	1.007 (1.000-1.015)	0.06
Carbohydrate intake, g	−0.002 (−0.846)	0.40	1.004 (0.998-1.009)	0.18
Fat intake, g	−0.015 (−2.152)	0.03	1.012 (0.997-1.027)	0.11
Medical history				
History of DM	−0.601 (−2.691)[a]	<0.01	1.280 (0.844-1.942)	0.24
Duration of DM, y	0.039 (2.121)[b]	0.03	0.984 (0.950-1.019)	0.38
History of HTN	−0.857 (−6.285)[a]	<0.01	1.892 (1.448-2.473)[a]	<0.01
Duration of HTN, y	−0.038 (−3.828)[a]	<0.01	1.034 (1.009-1.060)[a]	<0.01
Social history				
Smoking history	0.374 (3.336)[a]	<0.01	0.879 (0.725-1.067)	0.19
Physical activity	0.186 (3.637)[a]	<0.01	0.883 (0.808-0.964)[a]	<0.01
Reproductive factors				
Duration of menstruation, y	−0.026 (−0.856)	0.39	1.009 (0.968-1.051)	0.68
Duration of menopause, y	0.005 (0.186)	0.85	0.984 (0.940-1.030)	0.49
Past history of pregnancy	−0.546 (−1.451)	0.15	1.314 (0.582-2.963)	0.51
Duration of OC use, mo	0.001 (0.290)	0.77	0.998 (0.990-1.006)	0.61
History of HT use	0.222 (2.440)[b]	0.02	0.803 (0.676-0.954)[b]	0.01
Duration of HT use, mo	0.004 (1.628)	0.10	0.994 (0.989-0.999)[b]	0.02

Data were analyzed using Complex Samples General Linear Models and Complex Samples Logistic Regression.
Data are expressed as B unstandardized coefficients (*t* value) and odds ratio (95% confidence interval).
ASM/Wt, appendicular skeletal muscle mass divided by weight; DM, diabetes mellitus; HT, hormone therapy; HTN, hypertension; OC, oral contraceptive; OR, odds ratio.
[a]$P < 0.01$.
[b]$P < 0.05$.

received HT may contribute to statistical significance. In addition, the KNHANES did not assess whether participants who received HT did so currently or before the survey. Because use of HT was significantly associated with sarcopenia only in participants younger than 65 years, current use, but not previous use, may prevent the development of sarcopenia. The reasons for these associations remain unclear. Large-scaled cohort studies are required to confirm the effects of HT use on sarcopenia in older and/or obese postmenopausal women.

The present study had several limitations. First, its cross-sectional design prevented assessment of the causal relationship between HT use and sarcopenia. Second, data on HT use were retrospectively collected by health questionnaires. Self-reported history of HT use was not objective data, and it may have led to recall bias. In addition, we also could not rule out

TABLE 4. *Odds ratios of the prevalence of sarcopenia in postmenopausal women stratified by duration of hormone therapy in age and body mass index subgroups*

	No. participants (%)	Unadjusted model	Adjusted model
Age ≥65 y			
No HT use	1,222 (65.1%)	1 (Reference)	1 (Reference)
HT use 1-12 mo	58 (76.2%)	1.72 (0.86-3.43)	1.25 (0.60-2.63)
HT use ≥13 mo	55 (69.2%)	1.20 (0.53-2.71)	0.84 (0.39-1.81)
Age <65 y			
No HT use	1,081 (66.9%)	1 (Reference)	1 (Reference)
HT use 1-12 mo	143 (61.9%)	0.80 (0.56-1.15)	0.86 (0.60-1.23)
HT use ≥13 mo	110 (52.8%)	0.55 (0.37-0.83)[a]	0.56 (0.36-0.86)[a]
BMI ≥25 kg/m^2			
No HT use	1,151 (87.8%)	1 (Reference)	1 (Reference)
HT use 1-12 mo	86 (83.6%)	0.71 (0.35-1.43)	0.87 (0.40-1.87)
HT use ≥13 mo	70 (82.0%)	0.64 (0.31-1.32)	0.61 (0.28-1.31)
BMI <25 kg/m^2			
No HT use	1,152 (53.3%)	1 (Reference)	1 (Reference)
HT use 1-12 mo	115 (56.5%)	1.14 (0.76-1.70)	1.05 (0.71-1.55)
HT use ≥ 13 mo	95 (45.4%)	0.73 (0.48-1.11)	0.65 (0.42-1.00)[b]

Data were analyzed using Complex Samples Logistic Regression and are expressed as unweighted number (weighted prevalence) and odds ratio (95% confidence interval).
Model adjusted for age, age at menarche, age at menopause, duration of menstruation and menopause, number of pregnancies, past history of OC use, duration of OC use, past histories of DM and HTN, duration of HTN and DM, smoking history, physical activity, and energy intake (total, proteins, carbohydrates, and fats).
BMI, body mass index; HT, hormone therapy; DM, diabetes mellitus; HT, hormone therapy; HTN, hypertension; OC, oral contraceptive.
[a]$P < 0.01$.
[b]$P < 0.05$.

healthy user bias. Third, the KNHANES did not assess several important variables, including the type of HT use, the interval since ceasing HT, and whether participants were receiving HT currently or before the survey, preventing assessment of the effects of these variables on the prevalence of sarcopenia. Despite these limitations, however, the present study had several advantages, being a large-scale study showing that use of HT was associated with muscle mass and the prevalence of sarcopenia.

CONCLUSION

The present study showed that prolonged use of HT was associated with higher muscle mass and lower prevalence of sarcopenia in postmenopausal women.

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