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Hormone Replacement Therapy and Its Relationship with Skeletal Muscle Mass and Bone Mineral Density in Women from Western Mexico: Cross-Sectional Study

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Abstract: Background: Every year, 1.5 million women worldwide experience menopause and the associated changes that cause disability and dysfunction. There are multiple treatments focused on the symptoms; hormone replacement therapy (HRT) may be one that helps us reduce these changes. **Objectives**: the objective of this work was to assess the relationship between skeletal muscle mass and bone mineral density in postmenopausal women using hormone replacement therapy. **Methods**: Study design: cross-sectional study. A systematic assessment of clinical charts from postmenopausal women using hormone replacement therapy. Differences between low muscle mass and low bone mineral density were assessed; linear regression models were calculated to estimated the effect of body mass index, length of menopause, age, presence of comorbidities, physical activity and muscle mass have over those variables. **Results**: Bone mineral density was heavily influenced level of body mass index (aß: 0.015, 95% CI, 0.010, 0.019, p<0.001) and age (aß: -0.006, 95% CI, -0.010, -0.002, p=0.002); while muscle mass changes were associated with body mass index (aß: 0.548, 95% CI, 0.456, 0.640, p<0.001) and Age (aß: -0.081, 95% CI, -0.155, -0.006, p=0.034) **Conclusions**: The use of Hormone replacement therapy does not have a relation with the levels of muscle mass neither bone mineral density in postmenopausal women.

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Menopause is a natural process in which the ovaries ceases the production of reproductive hormones for at least 12 consecutive months[1]. Great proportion of women experience menopausal symptoms, which their nature and severity varies between individuals[2], most of menopausal women, up to 75%, have vasomotor effects such as hot flushes and night sweats[3], around half will present genitourinary symptoms, such as dysuria, vaginal dryness, urgency, itching and burning[3,4]; other common symptoms are loss of libido, depression, hair loss, joint pain; decreased bone mass density, muscle mass, and strength[4]. Reduced muscle mass is linked to the lack of Estradiol hormone, which role is to regulate menstrual cycle, also, it promotes muscle regeneration by stimulating the proliferative activity of the muscle cells[5]; subsequently, lean mass is replaced by fat increasing body weight, resulting in obesity[6]. Also, the reduced estrogen production correlates with an increase in proinflammatory cytokines leading to increased levels of oxidative stress which increases catabolism, thus leading muscle loss[7]. To relieve menopause symptoms hormone replacement therapy (HRT) is prescribed, conventional treatment includes an estrogen and progesterone component to mimic hormones synthetized by the human ovary[8]. Effectiveness of HRT to prevent muscle mass is still under debate, some works had reported greater retention of muscle levels or even enhanced muscle function[9–11]; while other had not showed any difference after prescribing HRT in postmenopausal women[12,13]. Also, HRT aids in preventing bone depletion, by reducing the resorptive activity and averting both increased osteoclast recruitment and delayed apoptosis[14,15]. Therefore, the objective of this work was to assess the relationship between skeletal muscle mass and bone mineral density in postmenopausal women using hormone replacement therapy.

2. Materials and Methods

2.1. Study Design and Clinical Stetting

Study design: cross-sectional study. Three trained researchers performed a systematic assessment of clinical charts from postmenopausal women using hormone replacement therapy who attended an outpatient rheumatology consultation therapeutic university Centre from 1 January 2017 to 31 December 2018. This study was performed from January 2024 to August 2024.

2.2. Inclusion and Exclusion Criteria

Patients included in this study were postmenopausal women, aged ≥ 40 years old, who voluntary signed an informed consent form. Patients were excluded if they had a body weight ≥ 150 kg. Also, they were excluded if they reported using on the following drugs 1 month previously to the study: antiresorptive drugs (bisphosphonates, denosumab and/or parathormone), calcium channel blockers, statins, and/or glucocorticoids (oral or injected). Lastly, patients who reported any of the following diseases were also excluded: Diagnosed chronic kidney disease, cancer, tuberculosis, hyperthyroidism or hypothyroidism, Cushing syndrome, hyperparathyroidism, and/or malabsorption syndrome.

2.3. Ethics

This study was approved by the following committees: Ethics in Research committee (CEI-CUCS) and Committee of Research (CI-CUCS) at the University Centre of Health Sciences (CUCS), University of Guadalajara, approval code CI-05623 (Approved 11 September 2023). This research protocol followed the Ethical Principles for Medical Research Involving Human Subjects described in the Helsinki Declaration.

2.4. Study Development

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Sociodemographic and clinical data were ascertained by three trained researcher who interviewed the patients who attended their clinical consultation. Information recollected was classified as:

(a) Sociodemographic variables: gender, age, body mass index, alcohol consumption, smoking, exercising habits, academic education. etc.

(b) Comorbid diseases: hypertension, diabetes mellitus type 2, obesity, other comorbid diseases.

(c) Pharmacological treatment: any drug chronically used by the patient (≥ 90 days), use of hormone replacement therapy (HRT).

All patients were assessed by Dual X-ray absorptiometry (DXA) by trained researcher to measure bone mineral density (BMD) and muscle mass (MM). To assess and compare the effect of HRT in BDM and MM, two groups were conformed: A) if patients were using HRT, and B) if patients did not use HRT in the last 90 days.

2.5. Statistical Analysis

To assess the relation between the use of HRT and skeletal muscle mass, we classified patients with low BMD as osteopenia (Z score between -2 to -3 SD) or osteoporosis (Z score < -3 SD). Independent Student's t-tests were used for comparisons of quantitative variables between groups; chi-square tests (or Fischer exact tests if required) were used for comparisons of proportions between groups. Correlation between quantitative variables was calculated using Spearman test. Univariate and multivariate regression models were used to assess potential predictors for low muscle mass and low bone mineral density respectively. The significance level was set at $p \leq 0.05$. The analyses were performed using the statistical software SPPS Statistics Version 24.

3. Results

A total of 248 females were assessed for this study, the mean age was 58.8 ± 7.4 years old, with a body mass index (BMI) of 27.8 ± 5.6. Less than half of these patients (42.3%) performed some kind of aerobic physical activity. The most common comorbidity observed were Hypertension (32.2%), Dyslipidemia (27.3%) and Diabetes Mellitus (18.7%). From these patients, 130 (53.0%) were using hormone replacement therapy, which in comparison to patients who did not receive hormone replacement therapy, had fewer years since their menopause and a higher proportion of patients using alcohol (Table 1).

Table 1. Comparison of sociodemographic characteristics.

Variable	Total n = 248 (%)	Use of Hormone replacement therapy n = 130 (%)	Without Hormone replacement therapy n = 118 (%)	p
Age, mean ± SD	58.8 ± 7.4	58.0 ± 6.1	59.7 ± 8.6	0.07
BMI. mean ± SD	27.8 ± 5.6	28.1 ± 5.4	27.5 ± 5.9	0.3
Menopause (years), mean ± SD	11.2 ± 7.9	9.9 ± 7.0	12.7 ± 8.6	0.006
Aerobic Physical activity*, n (%)	105 (42.3)	49 (37.4)	56 (47.9)	0.09
Alcoholism, n (%)	77 (31.4)	50 (38.2)	27 (23.5)	0.013
Smoking habit, n (%)	81 (33.0)	49 (37.4)	32 (27.4)	0.09
Hypertension, n (%)	79 (32.2)	45 (34.4)	34 (29.1)	0.3
Dyslipidemia, n (%)	67 (27.3)	38 (29.2)	29 (24.8)	0.4
Diabetes Mellitus, n (%)	46 (18.7)	21 (16.0)	25 (21.4)	0.2

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Muscle mass (kg), mean ± SD	40.7 ± 5.1	41.0 ± 5.2	40.4 ± 4.9	0.4
Z-score for BMD, mean ± SD	1.04 ± 0.16	1.05 ± 0.14	1.02 ± 0.18	0.1

*>150 min per weekAbbreviatures: BMD: Bone mineral density. Qualitative variables are expressed as frequencies and percentages; quantitative variables are expressed as mean and standard deviation (SD).

Table 2 shows the correlation between muscle mass and bone mineral density (BMD); regarding muscle mass there was a strong positive correlation between body mass index (r=0.617, p<0.001) and a moderate positive correlation between BMD spine (r=0.360, p<0.001). Regarding BMD, we found statistical significance in its correlation with BMI (r=0.323, p<0.001), age (r=-0.288, p<0.001) and menopause length (r=-0.194, p=0.002).

Table 2. Correlation between muscle mass and BMD.

Variable	Muscle mass		BMD spine	
	r	p	r	p
Muscle mass	---	---	0.360	<0.001
Age (years)	-0.124	0.053	-0.288	<0.001
Menopause length	0.011	0.8	-0.194	0.002
BMI	0.617	<0.001	0.323	<0.001
BMD spine	0.360	<0.001	---	---

Pearson correlation test.

Bone mineral density assessment

In table 3 is shown the comparison between patients who had low BMD vs patients with BMD by a central DXA. Patients who have low BMD were older, with lengthier menopause; additionally, they have lower BMI and lower muscle mass. Hormone replacement therapy did not show any effect on having low BMD (Table 3).

Table 3. Comparison with low BMD.

Variable	Low BMD n = 171 (%)	Normal BMD n = 77 (%)	p
Age, mean ± SD	60.3 ± 7.0	55.3 ± 7.3	<0.001
Menopause length (years), mean ± SD	12.3 ± 7.9	8.8 ± 7.3	<0.001
BMI, mean ± SD	26.9 ± 5.1	29.9 ± 6.3	<0.001
Physical activity, n (%)	68 (39.8)	37 (48.1)	0.2
Alcoholism, n (%)	59 (34.5)	18 (24.0)	0.1
Smoking habit, n (%)	58 (33.9)	23 (29.9)	0.5
Hypertension, n (%)	55 (32.2)	24 (31.2)	0.8
Dyslipidemia, n (%)	50 (29.2)	17 (22.4)	0.2
Diabetes Mellitus, n (%)	33 (19.3)	13 (16.9)	0.6
Hormone replacement therapy, n (%)	91 (53.2)	40 (51.9)	0.8
Low muscle mass, n (%)	48 (28.1)	41 (53.2)	<0.001

Qualitative variables are expressed as frequencies and percentages; quantitative variables are expressed as mean and standard deviation (SD).

Table 4 shows a linear regression model where the dependent variable was BMD spine, variables entered in the moder as cofounder were: BMI, menopause length, age, presence of comorbidities, use

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of hormone replacement therapy, aerobic physical activity, and muscle mass. In the unadjusted model both BMI (ß =0.013, 95% CI= 0.006, 0.019, p<0.001) and age (ß = -0.006, 95% CI= -0.011, -0.001, p=0.045) influence BMD spine. After adjusting for menopause, comorbidities, hormone replacement therapy, aerobic physical activity and muscle mass, still both BMI (ß =0.015, 95% CI= 0.010, 0.019, p<0.001) and age (ß = -0.006, 95% CI= -0.006, -0.002, p=0.002) influence BMD spine.

Table 4. Linear regression for BMD spine.

	BMD spine					
	Unadjusted			Adjusted		
	Enter Method			Stepwise method		
	ß	95% CI	*p*-Value	aß	95% CI	*p*-Value
Body mass index	0.013	0.006, 0.019	<0.001	0.015	0.010, 0.019	<0.001
Menopause (length)	-0.001	-0.006, 0.004	0.7	---	---	---
Age	-0.006	-0.011, -0.000	0.045	-0.006	-0.010, -0.002	0.002
Comorbidities	0.024	-0.036, 0.084	0.4	---	---	---
Hormone replacement therapy	-0.014	-0.072, 0.043	0.6	---	---	---
Aerobic physical activity	0.002	-0.055, 0.060	0.9	---	---	---
Muscle mass	0.003	-0.004, 0.010	0.3	---	---	---

Enter method: Adjusted R^2: 0.144, Std error: 0.21. Step-wise method: Adjusted R^2: 0.156, Std error: 0.21.

Table 5 shows a linear regression model where the dependent variable was muscle mass, variables entered in the moder as cofounder were: BMI, menopause length, age, presence of comorbidities, use of hormone replacement therapy, aerobic physical activity, and BMD spine. In the unadjusted model both BMI (ß =0.516, 95% CI= 0.416, 0.617, p<0.001) and age (ß = -0.128, 95% CI= -0.233, -0.024, p=0.016) influence muscle mass. After adjusting for menopause, comorbidities, hormone replacement therapy, aerobic physical activity, and BMD spine, still both BMI (ß =0.516, 95% CI= 0.416, 0.617, p<0.001) and age (ß = -0.081, 95% CI= -0.155, -0.006, p=0.034) influence muscle mass.

Table 5. Linear regression for muscle mass.

	Muscle Mass					
	Unadjusted			Adjusted		
	Enter Method			Stepwise method		
	ß	95% CI	*p*-Value	a ß	95% CI	*p*-Value
Body mass index	0.516	0.416, 0.617	<0.001	0.548	0.456, 0.640	<0.001
Menopause (length)	0.071	-0.021, 0.162	0.132	---	---	---
Age	-0.128	-0.233, -0.024	0.016	-0.081	-0.155, -0.006	0.034
Comorbidities	0.072	-1.059, 1.203	0.9	---	---	---
Hormone replacement therapy	0.034	-1.045, 1.113	0.9	---	---	---
Aerobic physical activity	-0.480	-1.563, 0.603	0.3	---	---	---
Bone mineral density spine	1.212	-1.263, 3.688	0.3	---	---	---

Enter method: Adjusted R^2: 0.378, Std error: 4.05. Step-wise method: Adjusted R^2: 0.380, Std error: 4.04.

4. Discussion

In this study we assessed the effect of using hormone replacement therapy (HRT) on muscle mass and bone mineral density in postmenopausal women. We did not observe any statistical relationship between them. Body mass index showed an additive effect on both BMD and muscle mass; whereas, an increasing in age reduced both variables.

In our sample, approximately half of the patients (52.4%) were receiving HRT, in our bivariate analysis its use did not show any significant statistical difference on muscle mass or BMD, neither did show any effect on a linear regression model. In a systematic review made by Javed A et al

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concluded that HRT had no beneficial or detrimental association with muscle mass[16]. Another systematic review by Yang X et al described that HRT did not show an effect in muscle mass[17]. However, Kim S and Kim R evaluated the effect of HRT in Korean women diagnosed with sarcopenia, observing that its prolonged use was associated with high muscle mass[18]. Another research by Sipilä S et al. compared the effect of exercise, HRT, exercise + HRT and a placebo in muscle mass on postmenopausal women, observing that the group using HRT improved muscle mass, although they benefit more while also doing high-impact physical training[19]. Therefore, the use of HRT to reduce muscle loss seems to be undefined yet.

Regarding BMD spine, in our study HRT did not show any effect on it, neither in bivariate analysis nor multivariate analysis. In a clinical trial by Zuo H et al, they followed Chinese women taking menopausal hormone therapy, finding that its use reduced bone turnover rate[20]. In a study by Sheedy A et al, compared the changes in bone turnover in women taking HRT and women who discontinued HRT in a period of 5 years, finding that those patients who discontinued the use of HRT had a decreased bone density while patients who kept using it maintained theirs levels[21]. Another study supporting these findings was realized by Cheng S et al, where they followed-up postmenopausal women using HRT for 1 year, where they found that the use of HRT maintained the levels of BMD[22] .

Strengths and Limitations

The present study focuses on the assessment of postmenopausal women and the relation of HRT with muscle mass and bone mineral density. Here we present a linear regression model for each variable taking into account common variables such as body mass index, presence of comorbidities and if they practiced aerobic physical activity. Also, none of the women analyzed in our sample were diagnosed with sarcopenia, therefore, our study shows the effect of HRT before a common condition in postmenopausal women start appearing. However, one of the main limitations in our study was the lack of follow-up, which make us unable to observe the effects at long term of the use of HRT.

5. Conclusions

The use of Hormone replacement therapy does not have a relation with the levels of muscle mass neither bone mineral density in postmenopausal women. Further studies are needed to help us establish the relationship between the use of hormone replacement therapy and its effect on skeletal muscle mass and bone mineral density. Physicians treating these patients should consider other options.

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Informed Consent Statement: Patient consent was waived due to this study being retrospective based on the review of clinical charts. This study did not involve confidential information and any possible identifiers, such as name, address, code, etc., of the patients were removed from the database before the analysis and interpretation.

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Data Availability Statement: The dataset supporting the conclusions presented in this article is available on request from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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