Low-dose tibolone (1.25 mg/d) does not affect muscle strength in older women

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Abstract

Objective: More than 50% of all fractures occur in people without osteoporosis. Hormone therapy increases bone density, improves postural balance, and reduces fracture risk in postmenopausal women. It is unclear whether tibolone, a synthetic steroid hormone drug, can improve muscle strength. Thus, the aim of this study was to study the effects of low-dose tibolone therapy on muscle strength in older women.

Methods: Eighty healthy women (69 completed the study) 60 years or older were recruited through advertising in the local media. They were randomly allocated to receive either tibolone 1.25 mg/day or placebo for 6 months. The stand-up test was used to assess leg muscle strength and balance. Handgrip and leg muscle strength were measured using JAMAR and modified Cybex dynamometers.

Results: Baseline characteristics, including serum estradiol values and muscle strength, were similar in the two groups. Compliance with the therapy regimen was very high, averaging more than 97% in both groups. After 6 months, mean values for handgrip strength, knee extensor strength, and average time to perform 10 stands were improved numerically in both groups compared with values during baseline. However, there were no significant differences in these parameters within or between groups, and differences remained nonsignificant after adjustment for age, serum estradiol, and baseline value.

Conclusions: Short-term treatment with low-dose tibolone (1.25 mg/d) seems not to affect muscle strength in older women.

Key Words: Hormone therapy – Estrogens – Tibolone – Menopause – Elderly – Muscle strength.

Falls are common in the aging population. In the course of 1 year, approximately 30% of the population older than 65 years and 59% of the population older than 85 years will fall at least once.^{1,2} It has been estimated that falls account for 10% of all visits to emergency departments and 6% of urgent hospitalizations in older persons.² Hip fractures are one of the more serious consequences of falls; approximately 1% of all falls in older persons will result in a hip fracture.³⁻⁵ Muscle strength, balance, vision, and functional capacities, traits that have been suggested as predictive

of the risk for falls and fractures, deteriorate with age.⁶ Interventions to prevent falls in older adults are therefore very important.⁷ Multiple-component group exercise regimens reduce the incidence of falls and the risk of falling, as do tai chi and individually prescribed multicomponent home-based exercise programs.⁸ Postmenopausal hormone therapy (HT) increases bone mass,⁹ improves postural balance,¹⁰⁻¹² and reduces fracture risk,¹³ but the risk of fracture returns rapidly to baseline after stopping therapy.¹⁴⁻¹⁷

Whether HT in older women can improve postural balance and/or muscle strength and function, and thus reduce the risk of falls and fracture, is a very important question because most fractures occur in older people. Tibolone is a tissue-selective agent with combined estrogenic, androgenic, and progestogenic effects.¹⁸ Recently, we reported that low-dose tibolone did not substantially improve postural balance in older women.¹⁹ However, the Long Term Intervention on Fractures with Tibolone (LIFT) study showed that low-dose tibolone (1.25 mg/d) significantly reduced the risk of vertebral and nonvertebral fractures in older osteoporotic women.²⁰

The influence of HT on muscle strength is currently under debate. Some randomized controlled studies show an increase in muscle strength with HT,²¹⁻²⁴ whereas others show no effect.^{25,26}

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TABLE 1. Baseline characteristics of participants in the two study groups

Baseline characteristics	Tibolone (n = 40)	Placebo (n = 40)
Age, y	67.4 (5.2)	68.5 (5.1)
Age at menopause, y	50.2 (3.5)	50.3 (4.2)
Years since menopause	17 (6.7)	18.2 (6.8)
Body mass index, kg/m ²	25.7 (2.9)	24.9 (3.3)
Estradiol/Serum level, pmol/L ^a	79.1 (13.3)	76.4 (14.9)
Systemic HT ever use, no. (%)		
No	30 (75%)	31 (77%)
Yes	10 (25%)	9 (23%)

Data are presented as mean (SD), unless otherwise stated.

HT, hormone therapy.

^aDetection limit: 25 pmol/L.

The aim of this study was to examine the short-term effects of low-dose tibolone on muscle strength in older women and to compare these results with those of women of similar age who received placebo. The dose of tibolone of 1.25 mg/day, half the standard dose, was chosen because of the documented effects of this dose in preserving bone mass early after menopause²⁷ and in older osteopenic women²⁸ and, recently, in reducing fracture risk in older osteoporotic women.²⁰

METHODS

In this randomized, double-blind, placebo-controlled study, 80 white women 60 years or older and with a body mass index (BMI) between 18 and 30 kg/m² were recruited through advertising in the local media in Uppsala, Sweden. We excluded women who had been exposed to medium-potency HT or vaginal 17 β -estradiol during the previous 6 months and those in whom HT was contraindicated (eg, with a known or suspected estrogen-dependent cancer, an increased risk of thromboembolic disease, or suspected cardiovascular disease). Women with hypertension (170/105 mm Hg), those using drugs known to affect postural balance (eg, sedative-hypnotic agents or antiepileptic drugs), and those with impaired locomotion or auditory or visual function were also excluded (glasses were allowed). In total, 19 women had been receiving some form of HT before inclusion in the study, with a mean time since exposure of 6.5 years.

Participants were randomized to double-blind treatment with active tibolone 1.25 mg/day or identical placebo for 6 months. Randomization was achieved with computer-generated assignment in blocks of 10, using sealed numbered treatment preparations that were prepared by the hospital pharmacy and consecutively dispersed after enrollment of each participant. Follow-up assessments were carried out at 6 months.

All participants gave their informed consent. The study was approved by the ethics committee of the Faculty of Medicine, Uppsala University.

Measurements of muscle strength and function were assessed by the same examiner (P.S.) at baseline and at the 6-month follow-up. Handgrip strength was measured using a JAMAR hydraulic hand dynamometer (5030J1). Both hands were tested three times using the best results for each hand in the comparison. The measurement was performed in the sit-

ting position with the arm held in a comfortable position as described by Spijkerman et al.²⁹ Maximum strength was expressed in kilograms.

Isokinetic knee flexion and extension strength were measured using a Cybex II dynamometer (Lumex Corp., Bay Shore, NY) with a modified lever arm (Aero Technical Corp., Stockholm, Sweden, devised by Knutsson and Litton), using an examination table (Alfex). Calibration of the Cybex II has been described elsewhere.²² The participants were strapped in a sitting position with adjustable belts around the thigh and chest. The axis of the lever arm of the dynamometer was adjusted in relation to the axis of the knee joint. The measurement was from full extension (0°) to 90° of knee flexion and back to full extension. The participants performed three maximal voluntary contractions at 90°/second. The peak torque produced by each leg, expressed in Newton meters (Nm), was considered the best indicator of knee flexion and extension strength and was used for the comparison, as this has proven to be a highly reproducible variable in previous studies.³⁰ The best values from knee flexion and extension were added and used in the comparison as leg strength.

The timed-stands test was performed using a straight-backed chair without arms, with a seat height of 45 cm. The chair was placed against a wall for added stability. Participants were seated in a position allowing them to place their feet squarely on the floor in front of them, with knees flexed to slightly greater than 90° (so that their heels were somewhat closer than the back of the knees to the chair). The arms were crossed over the chest and the participant was to stand from the sitting position to full standing and then return to the sitting position again. The procedure was demonstrated to the participant beforehand. The examiner stood in front of the participant during the procedure. A test was successful if the participant could perform 10 stand-ups in a row. The test was performed once and expressed in seconds taken to perform 10 stand-ups.

BMI was calculated as the weight of the participant in kilograms divided by the square of her height in meters squared. Serum samples were drawn at baseline in the morning between 8 A.M. and 10 A.M., after an overnight fast, and were analyzed for serum estradiol concentration at the Department of Clinical Chemistry, using the AutoDelphia Estradiol kit (Wallac OY, Turku, Finland), with total coefficients of variation of 5.3%. The detection limit was 25 pmol/L.

The sample size was considered adequate to detect clinically significant effects and for comparison with previous reports, one of which had a similar sample size and demonstrated an effect on muscle strength from tibolone 2.5 mg/d in younger postmenopausal women.²⁴

The paired *t* test was used for within-group changes over the study period. A two-sample *t* test was applied as crude analysis. Analysis of covariance was used to adjust for slight baseline imbalances, with actual changes from baseline as a dependent variable, treatment as factor, and age, estrogen level, and parameter value at baseline as covariates. Non-parametric analysis based on Wilcoxon ranks was used as

TABLE 2. Changes over the 24-week study period for mean handgrip strength, knee extensor strength, and timed-stands tests: intention-to-treat analysis, within and between the study groups

Muscle strength parameter	Tibolone (n = 34)	Placebo (n = 35)	Crude group difference
Mean handgrip strength, kg	27.2 (4.7)	26.4 (4.1)	
Change	0.63 (2.83)	0.60 (2.36)	0.03 (−1.21 to 1.26) ^a
P value	0.19	0.14	
Mean knee extensor strength, Nm	142 (23)	133 (22)	
Change	2.49 (9.35)	0.96 (9.85)	1.53 (−3.02 to 6.07) ^a
P value	0.12	0.57	
Timed-stands test, s	19.3 (4.1)	20.5 (5.5)	
Change	−0.84 (2.45)	−1.44 (2.85)	0.60 (−0.66 to 1.86) ^a
P value	0.046	0.005	

There were no significant differences for any of the within- or between-group analyses after adjustment. Data are shown as mean (SD) or mean (95% CI).

^aAnalysis adjusted for age, estrogen level, and baseline parameter values.

appropriate. All analyses were performed using SAS Version 8.2 on a personal computer under Windows NT.

RESULTS

The two groups were similar in baseline characteristics, including serum estradiol values and muscle strength (Table 1). Of the 80 randomized women, 69 completed the study. Six women discontinued tibolone for one of the following reasons: never took any study medication, abdominal pain, headache, nausea/depression, lack of time, and unknown. Five women discontinued placebo (hypertension, headache/nausea, foot fracture, nausea/depression, and death from subdural hematoma). On average, the overall compliance was very high, more than 97% in both groups.

At baseline, there was no significant association between serum estradiol levels and muscle strength parameters. After 6 months, both study groups had improved versus baseline with regard to mean handgrip strength, knee extensor strength, and average time for 10 stands. However, none of these changes was significant, and the changes did not differ significantly between the study groups. In addition, all the within- and between-group analyses remained nonsignificant after adjustment for age, serum estradiol level, and parameter value at baseline (Table 2).

DISCUSSION

There was a numerical improvement in all measured muscular values (handgrip and knee extensor strength, and timed stands) after 6 months of low-dose tibolone (1.25 mg/d) therapy. However, similar changes were found in the control group (there were no significant differences between the study groups). This indicates that the observed improvements probably reflect an improved ability to perform the test the second time.

The lack of effect of low-dose tibolone on muscle strength in this study is in accordance with our previous report²⁶ on conventional continuous-combined HT for 6 months in women of similar age (all were >60 y; mean age, 67 y). The results of that study also indicated no significant differences in muscle strength, compared with those in the placebo group.²⁶ In addition, in 116 postmenopausal women (45–70 y), there were no improvements in muscle performance or balance or a reduction in falls after 48 weeks of HT.²⁵ Furthermore,

changes in lower body muscle strength were no different in 37 healthy older women (mean age, 69 y) after long-term use of conjugated estrogens from those in 48 women who did not take menopausal hormones.³¹ In contrast, in a randomized, placebo-controlled study in women soon after menopause, with a mean age of 54 years, tibolone 2.5 mg/day for 6 months improved handgrip strength and isometric knee extension strength (after adjustment for BMI)²⁴ but did not improve explosive leg extensor power or get-up-and-go tests.³² Furthermore, a randomized, open study in women (mean age, 60 y) showed a significant improvement in abductor pollicis muscle strength after 6 to 12 months of conjugated estrogens combined with norgestrel, compared with results in non-users.²² Also, two reviews, of which one was a recent meta-analysis, have demonstrated small but beneficial effects of HT on muscle strength.^{33,34}

The lack of effect in this study could have been the result of low power, the older age of the women at intervention, the low dose of tibolone (1.25 mg/d), the short duration of treatment, or differing effects of tibolone on muscle strength compared with conventional estrogen-progestin. In the two previous reports on tibolone,^{24,32} the sample size was similar to ours (85 vs 80 women), and improvement was registered after 6 months of therapy, which was the duration of our study. However, the mean age (54.2 y) was substantially lower in the previous studies and the dose of tibolone used (2.5 mg/d) was higher, twice that used in our study. It seems to be easier to affect some outcomes if treatment is undertaken close to menopause, as previously described for postural balance function¹¹ and progression of atherosclerosis in the artery wall.^{35,36} Proximity to menopause could therefore explain the positive effects of tibolone on muscle strength in the previous report.²⁴ In the other report on tibolone,³² values were improved in both the active and placebo groups, as in our study. The participants who did not complete our study were slightly, but not significantly, older than the rest but were otherwise very similar to those who completed the study. If it is indeed easier to improve muscle strength at a younger age, the slightly higher mean age in those not completing the study would not have spuriously affected our results.

In addition, the results of our study support those from previous studies indicating that timed stands and the get-up-and-go test are not influenced by tibolone.³²

In this study, there was no significant association between baseline serum estradiol levels and muscle strength parameters. However, the estradiol assay used in this study had a detection limit of 25 pmol/L, which might be too high to be useful for postmenopausal women older than 60 years; a lower detection limit might have uncovered an association. The discrepancy in findings between different studies could indicate that positive effects on muscle strength are possible closer to menopause. However, achievable effects on muscle strength in older persons seem minor and probably do not explain the reduced fracture risk reported after low-dose tibolone in older osteoporotic women.²⁰

CONCLUSIONS

In this study, short-term low-dose tibolone therapy (1.25 mg/d) did not significantly affect muscle strength in older women, compared with placebo recipients. However, this study did not address the potential effects on muscle strength in women at ages closer to menopause, using conventional tibolone doses (2.5 mg/d), or the effects of longer duration of therapy; these could be the focus of future studies.

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